THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 1 January 1988

In this issue:

Developmental Psychiatry Comes of Age
By John Bowlby

Significance and Meaning of
Neurological Signs in Schizophrenia
By Douglas W. Heinrichs and Robert W. Buchanan

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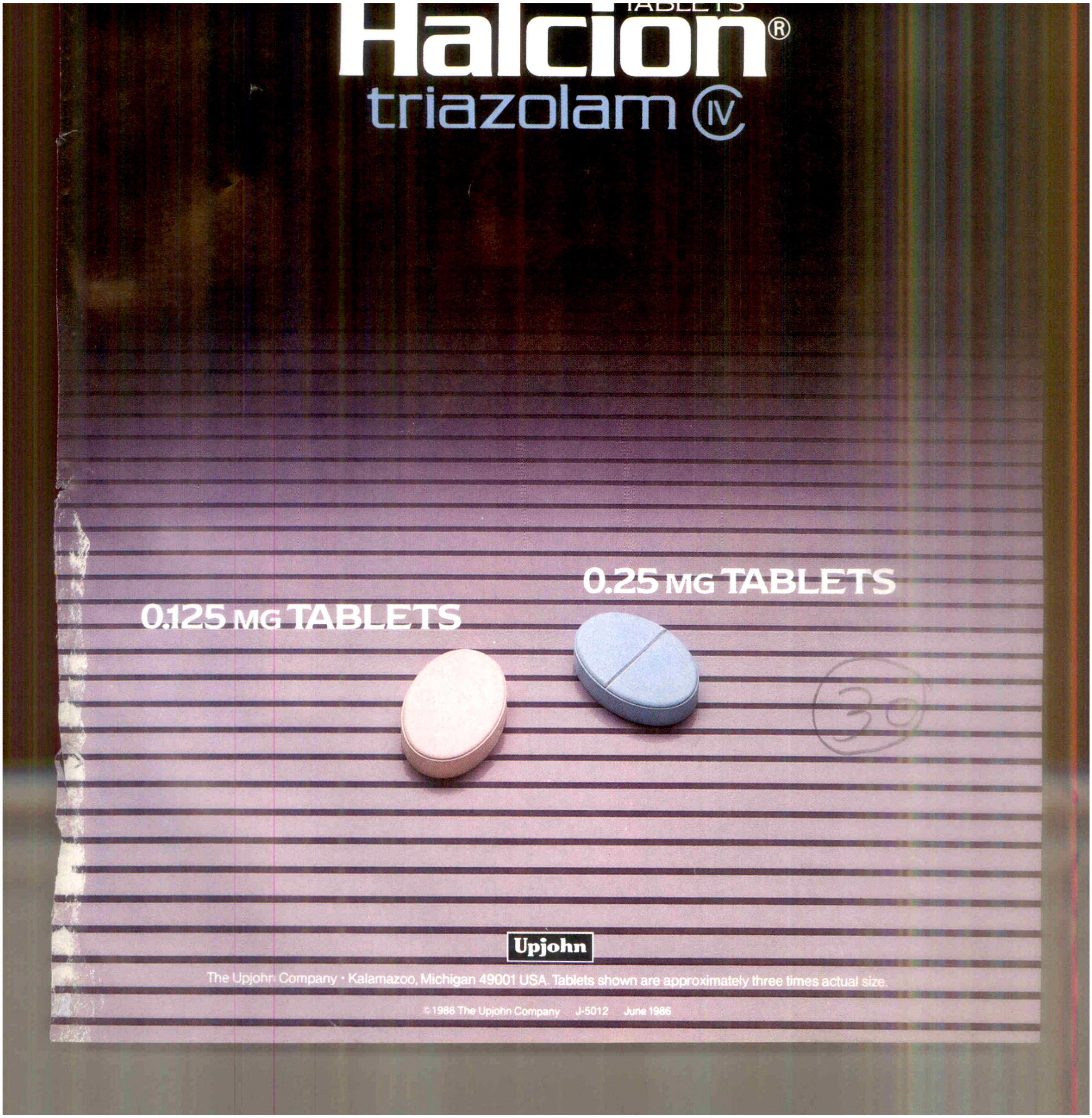

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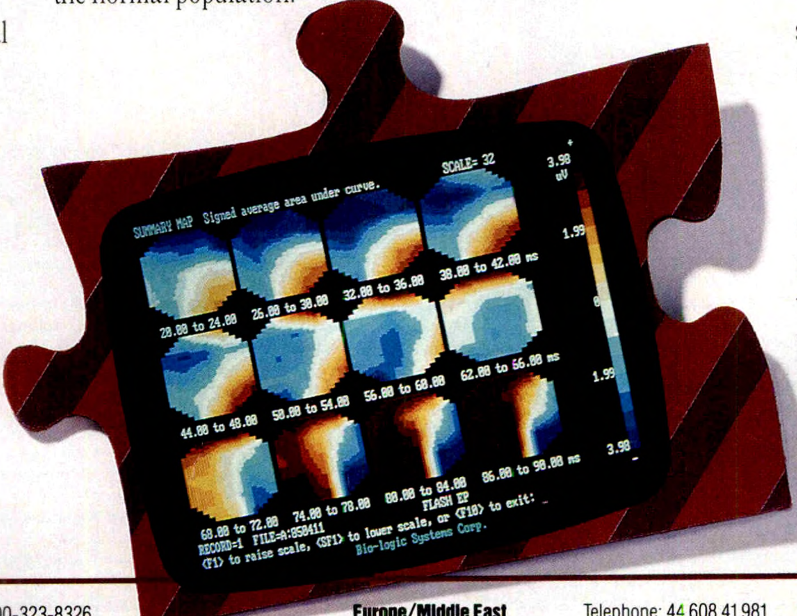

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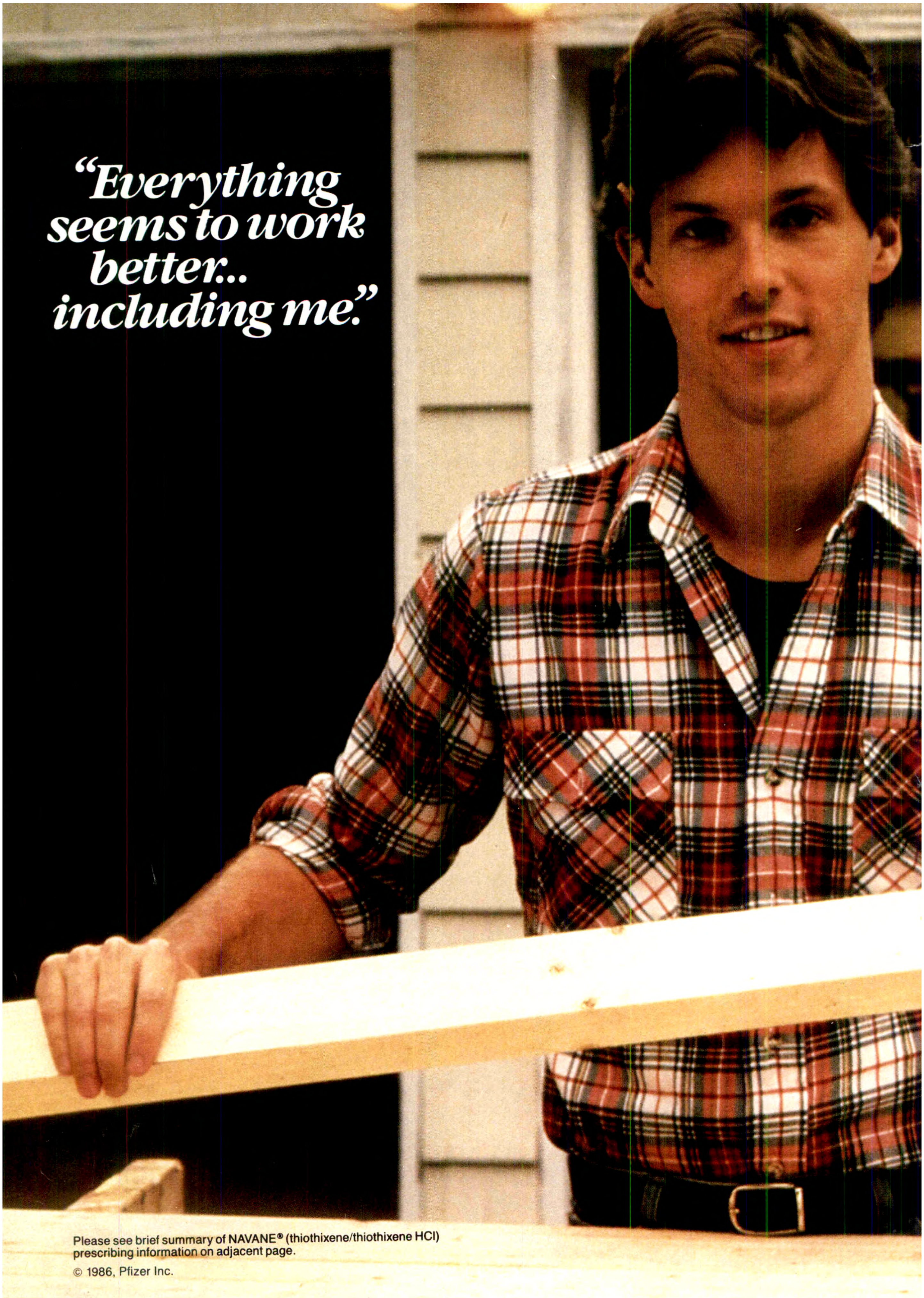
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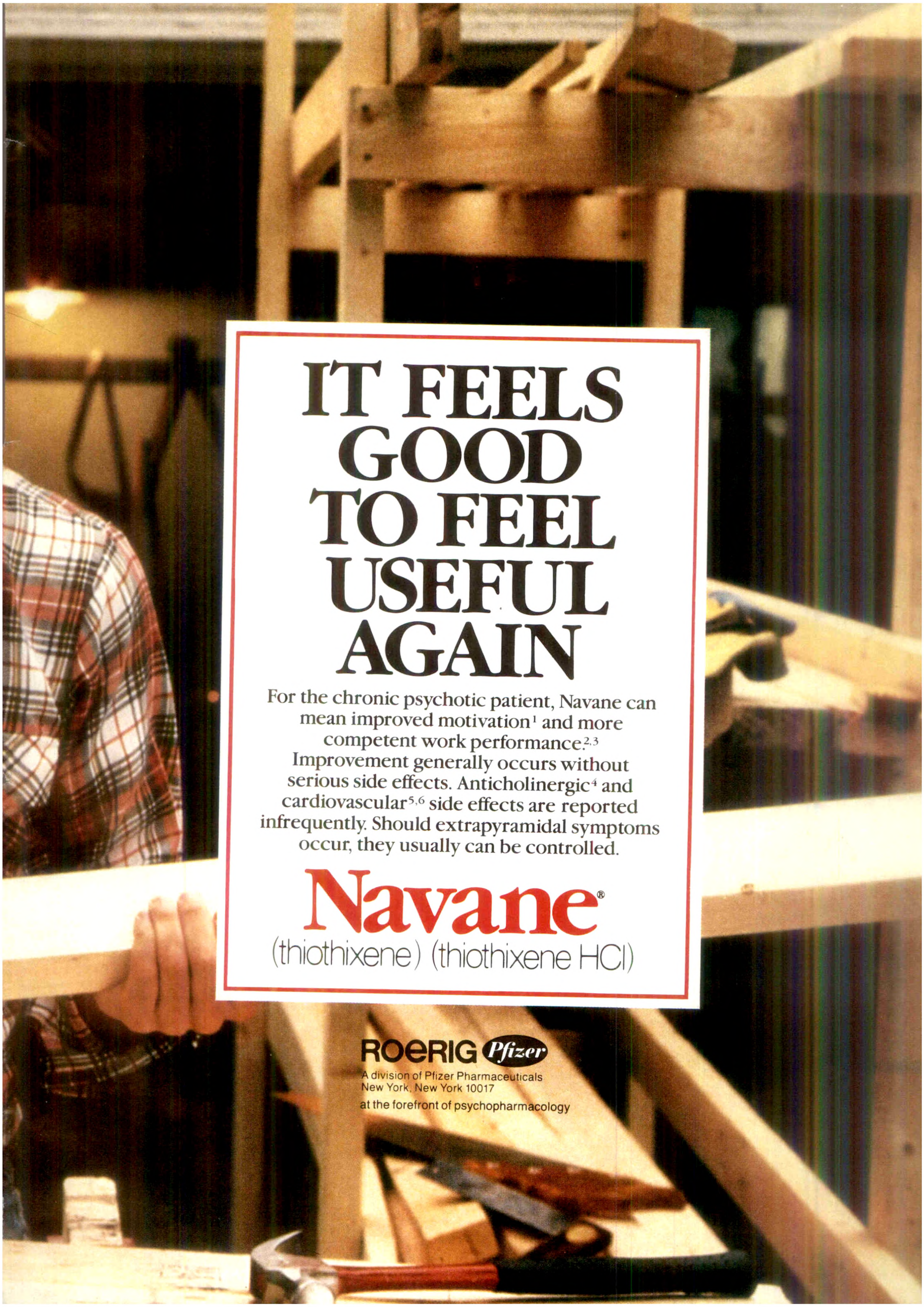

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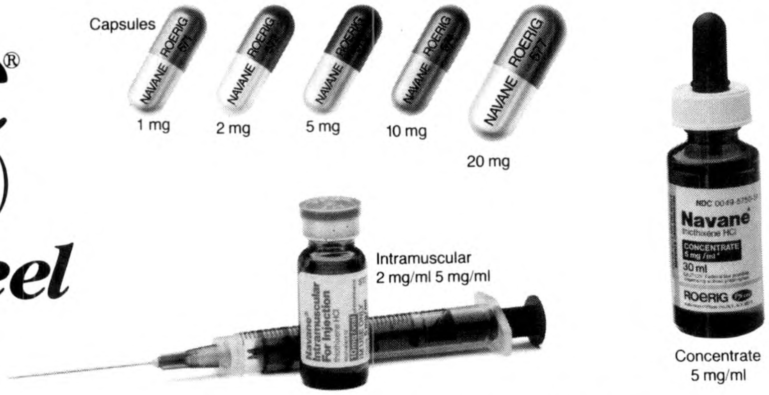

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Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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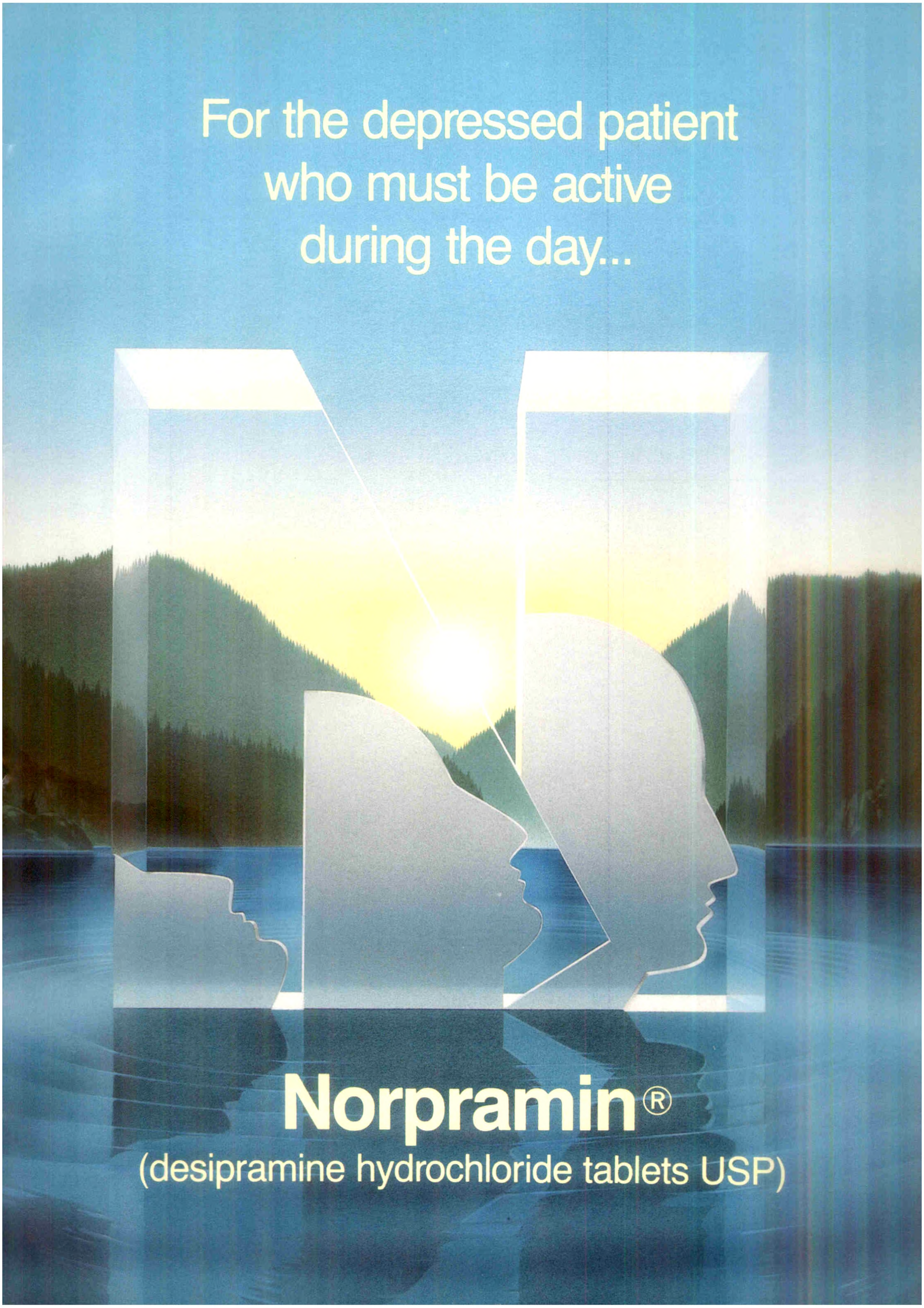
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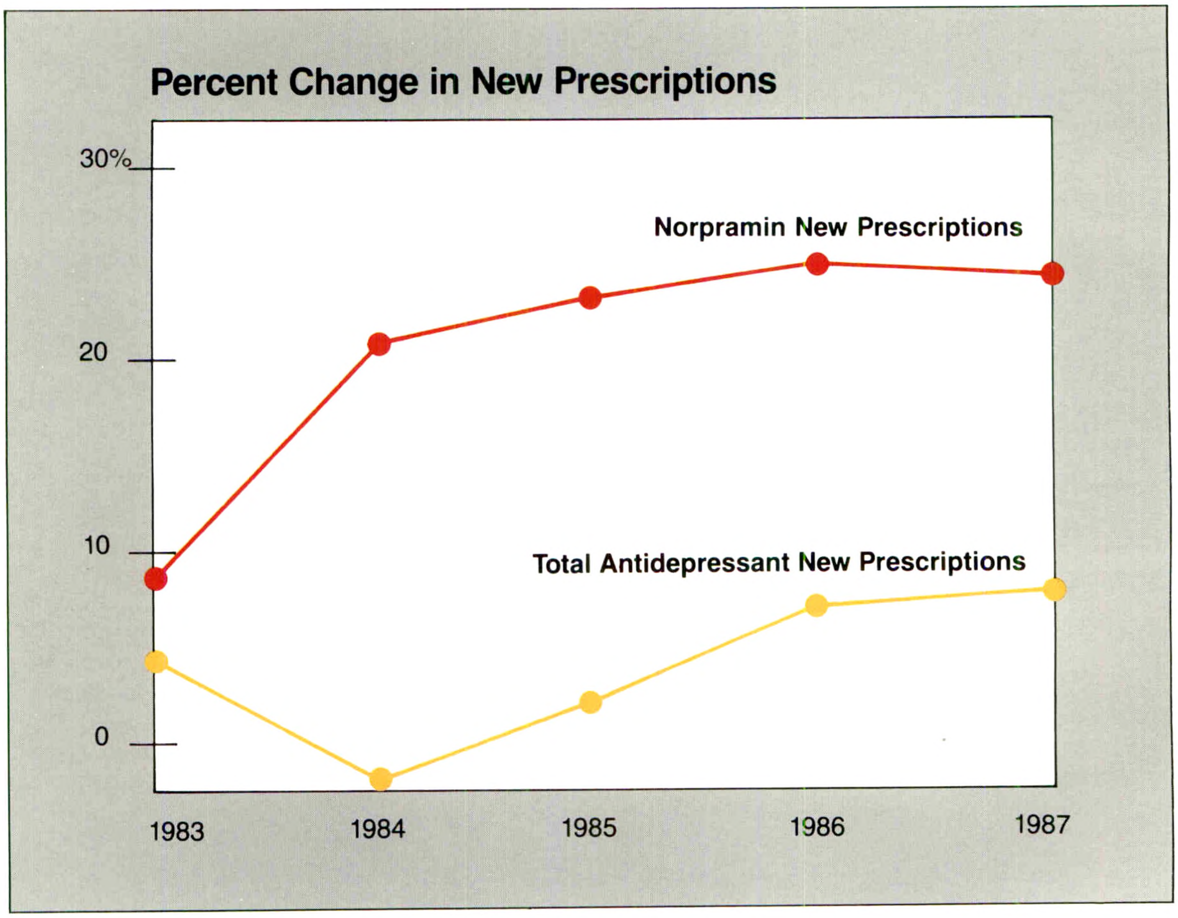

Percent Change in New Prescriptions

Figure 1. The red line tracks the percent change in new Norpramin prescriptions. The yellow line represents the total new prescription activity for the antidepressant market (based on data from a national prescription audit through July 1987).

Merrell Dow

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

a logical choice among antidepressants

The reasons are clear

- A 23-year record of efficacy in relieving symptoms of depression, including somatic anxiety,[1] sleep disturbances[2]
- Less anticholinergic activity than amitriptyline or doxepin, as shown in studies in the laboratory[3] and in normal human subjects[4,5] (see Warnings)
- Usually no excessive daytime drowsiness* (see Warnings)
- A well-defined clinical profile
- Unexcelled dosage flexibility, for patient convenience and compliance, for cost savings to patient...

*Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

References:

1. Nelson JC, Mazure C, Quinlan DM, and Jatlow PI: Drug responsive symptoms in melancholia. Arch Gen Psychiat 1984; 41:663-668.
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See Prescribing Information on the next page

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

Convenient choice of 6 tablet strengths and once daily or divided dosage allows titration to individual response

10 mg　25 mg　50 mg　75 mg　100 mg　150 mg

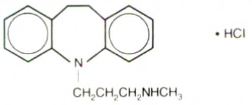
Norpramin®

(desipramine hydrochloride tablets USP)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Norpramin (desipramine hydrochloride USP) is an antidepressant drug of the tricyclic type, and is chemically: 5*H*-Dibenz [*b*,*f*] azepine-5-propanamine, 10, 11-dihydro-***N***-methyl-, monohydrochloride



INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: ACAcia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, *Metabolism*). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
    NDC 0068-0007-01: bottles of 100
25 mg yellow coated tablets imprinted **MERRELL** 11 or **NORPRAMIN** 25
    NDC 0068-0011-01: bottles of 100
    NDC 0068-0011-61: unit dose dispenser of 100
    NDC 0068-0011-10: bottles of 1000
50 mg green coated tablets imprinted **MERRELL** 15 or **NORPRAMIN** 50
    NDC 0068-0015-01: bottles of 100
    NDC 0068-0015-61: unit dose dispenser of 100
    NDC 0068-0015-10: bottles of 1000
75 mg orange coated tablets imprinted **MERRELL** 19 or **NORPRAMIN** 75
    NDC 0068-0019-01: bottles of 100
100 mg peach coated tablets imprinted **MERRELL** 20 or **NORPRAMIN** 100
    NDC 0068-0020-01: bottles of 100
150 mg white coated tablets imprinted **MERRELL** 21 or **NORPRAMIN** 150
    NDC 0068-0021-50: bottles of 50

Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect from excessive heat.

Product Information as of April, 1987　Y2900

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

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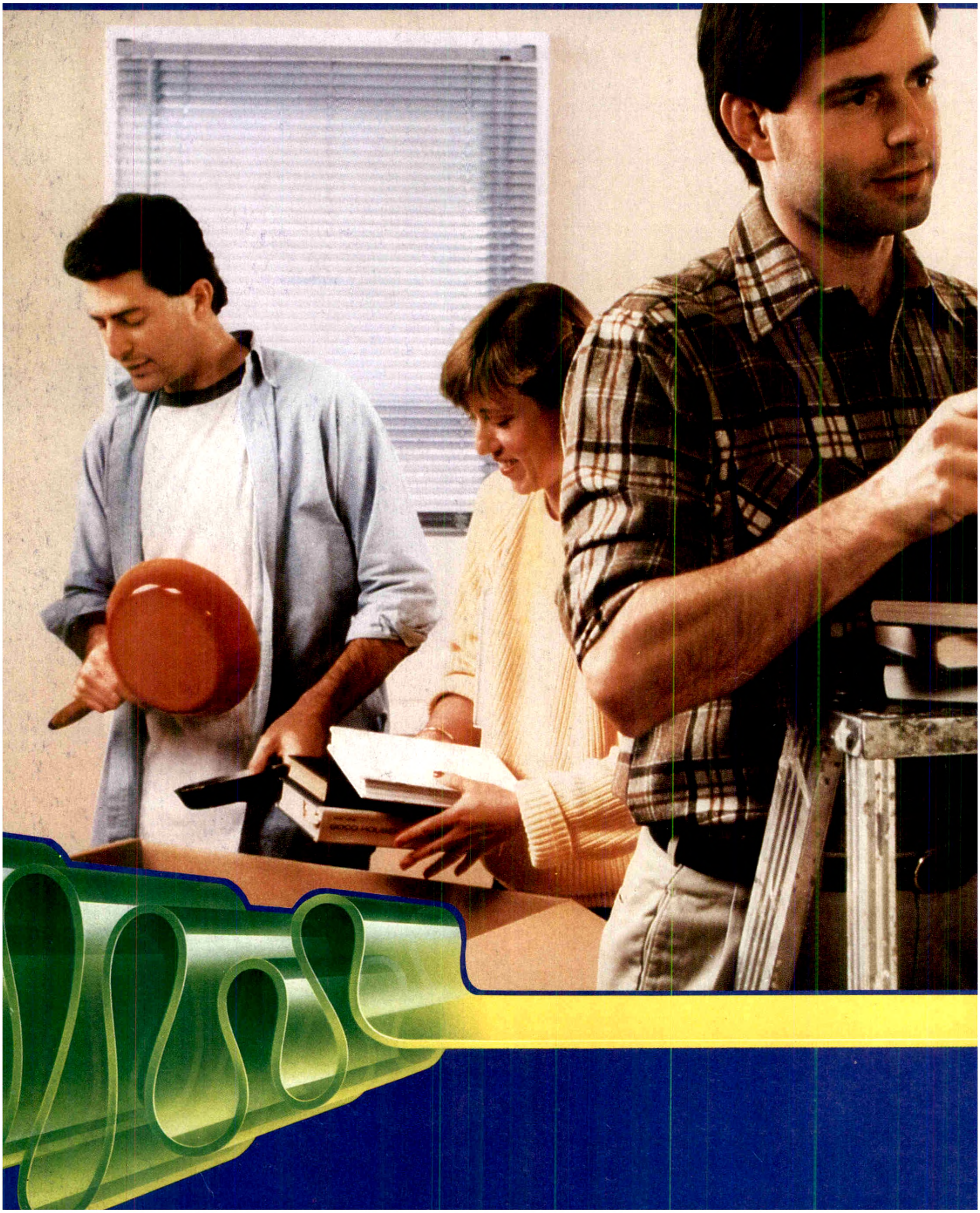

For the schizophrenic patient

Sustained protection from relapse

About 60% of schizophrenic patients will experience relapse at some time.[1] Because of the increased risk of deterioration with each relapse, today's therapeutic challenge is to use all available measures to prevent its occurrence.[2] The sustained drug delivery of once-monthly HALDOL Decanoate Injection can be one factor in reducing the risk of relapse. Monthly administration assures that patients receive the prescribed dose of medication.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

References:
1. Johnson DA: Epidemiological evaluation of maintenance antipsychotic treatment, in Tognoni G, Bellantuono C, Laher H (eds): *Epidemiological Impact of Psychotropic Drugs.* Amsterdam, Elsevier/North Holland Biomedical Press, 1981, pp 205-220.
2. Lehmann HE, Cancro R: Schizophrenia: clinical features, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry*, ed 4. Baltimore, Williams & Wilkins, 1985, vol 1, pp 680-713.

Please see brief summary of Prescribing Information on next page.

Once-monthly

HALDOL® DECANOATE

(HALOPERIDOL) INJECTION

McNEIL
PHARMACEUTICAL

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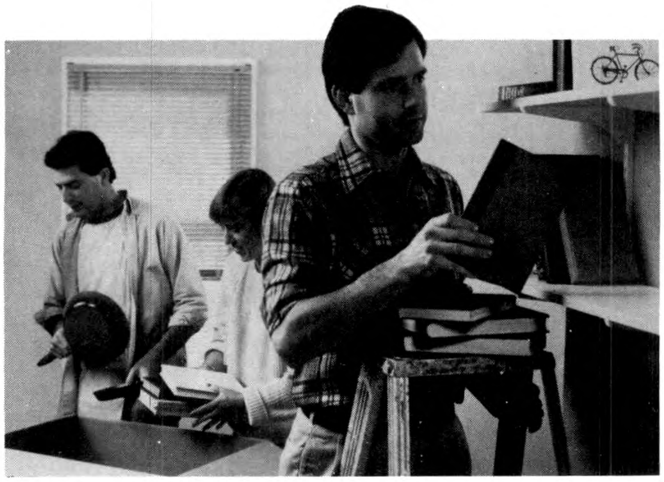

HALDOL® DECANOATE

(HALOPERIDOL) INJECTION

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause
allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especial
in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or drivir
may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely f
early evidence of neurological toxicity and treatment discontinued promptly if such sigr
appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable
potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperid
decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to
mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months
In the rat study survival was less than optimal in all dose groups, reducing the number of rats
risk for developing tumors. However, although a relatively greater number of rats survived to th
end of the study in high dose male and female groups, these animals did not have a great
incidence of tumors than control animals. Therefore, although not optimal, this study doe
suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats
doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mic
at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was
statistically significant increase in mammary gland neoplasia and total tumor incidence; at 2
times the same daily dose there was a statistically significant increase in pituitary glar
neoplasia. In male mice, no statistically significant differences in incidences of total tumors
specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administr
tion. Tissue culture experiments indicate that approximately one-third of human breast cance
are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs
contemplated in a patient with a previously detected breast cancer. Although disturbances suc
as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinic
significance of elevated serum prolactin levels is unknown for most patients. An increase
mammary neoplasms has been found in rodents after chronic administration of antipsychot
drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have show
an association between chronic administration of these drugs and mammary tumorigenesis: th
available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely
become pregnant has not been established; use only if benefit clearly justifies potential hazarc
to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscul
administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperid
Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, th
adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with
injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions ha
been reported frequently, often during the first few days of treatment. Generally they involve
Parkinson-like symptoms which when first observed were usually mild to moderately severe ar
usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akat
sia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, b
were often more severe. Severe extrapyramidal reactions have been reported at relatively lo
doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively hi
doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs m
be required. Persistent extrapyramidal reactions have been reported and the drug may have to
discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation
short-term antipsychotic therapy is generally uneventful. However, some patients on maintenan
treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases the
are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradu
withdrawal will reduce the occurrence of these signs, but until further evidence is availa
HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agen
HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndro
consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in so
patients on long-term therapy or may occur after drug therapy has been discontinued. The ri
appears to be greater in elderly patients on high-dose therapy, especially females. The sympto
are persistent and in some patients appear irreversible. The syndrome is characterized
rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongu
puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be acco
panied by involuntary movements of extremities and the trunk. There is no known effecti
treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms
this syndrome. It is suggested that all antipsychotic agents be discontinued if these sympto
appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent,
switch to a different antipsychotic agent, this syndrome may be masked. It has been reported th
fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if t
medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardi
dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia
characterized by delayed onset of choreic or dystonic movements, is often persistent, and has t
potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, eupho
agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, a
exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral stat
which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke ha
been reported with HALDOL. (See WARNINGS for further information concerning NM
Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes. *Hematol*
gic Effects: Reports of mild, usually transient leukopenia and leukocytosis, minimal decreas
in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocyto
rarely reported and only in association with other medication. *Liver Effects:* Impaired li
function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactio
isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorg
ment, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperg
cemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipati
diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mou
blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryng
spasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retin
pathy and visual disturbances. *Other:* Cases of sudden and unexpected death have be
reported in association with the administration of HALDOL. The nature of the evidence make
impossible to determine definitively what role, if any, HALDOL played in the outcome of t
reported cases. The possibility that HALDOL caused death cannot, of course, be excluded,
it is to be kept in mind that sudden and unexpected death may occur in psychotic patients wh
they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate
administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing inform
tion.

The short-acting HALDOL injectable form is intended only for acutely agitated psycho
patients with moderately severe to very severe symptoms.

6/3/

For additional information, please call:
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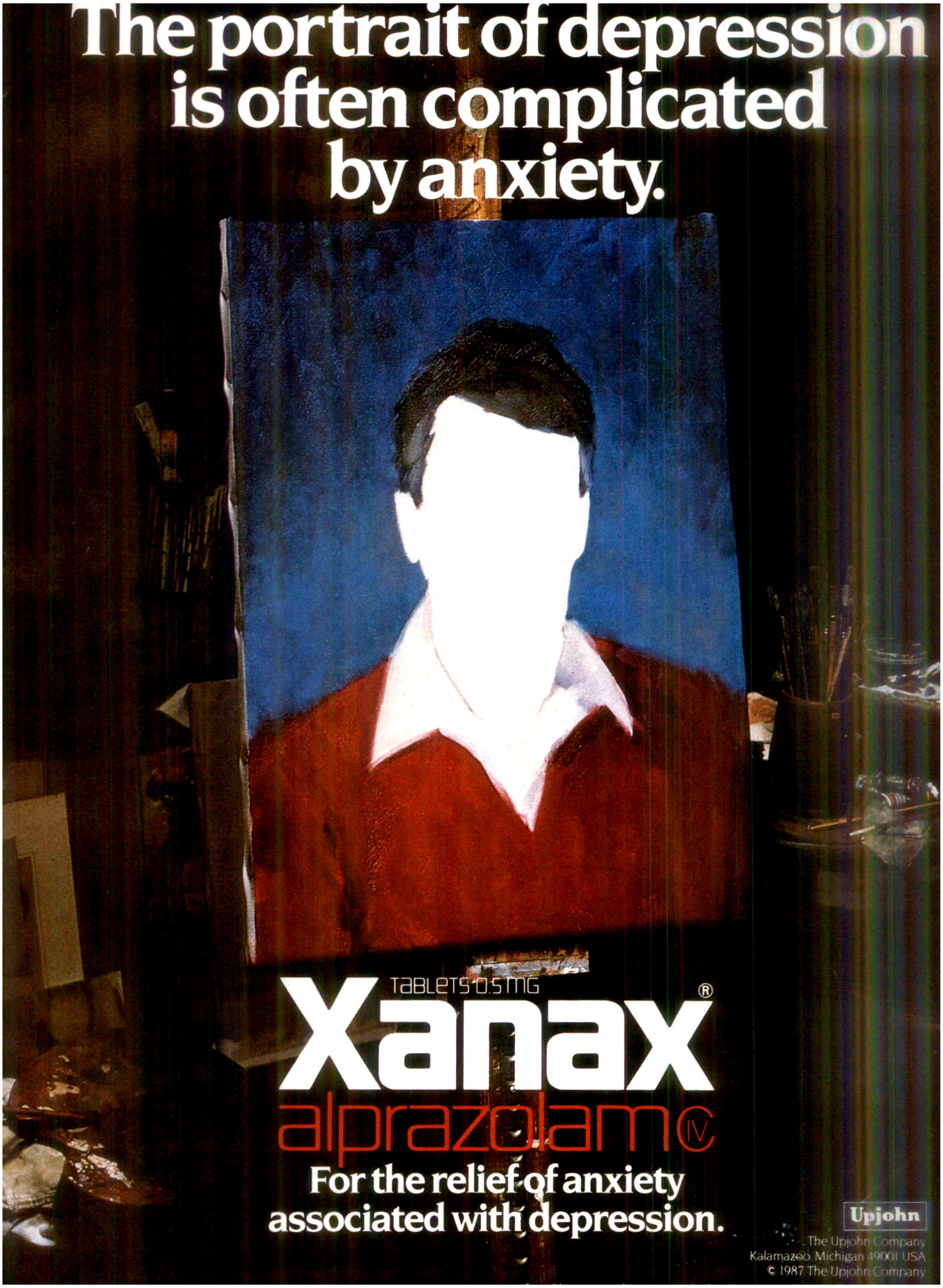

The portrait of depression is often complicated by anxiety.

TABLETS 0.5 MG

Xanax®

alprazolam Ⓘⓥ

For the relief of anxiety
associated with depression.

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XANAX® Tablets
(alprazolam, Ⓒ)

INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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September 1987

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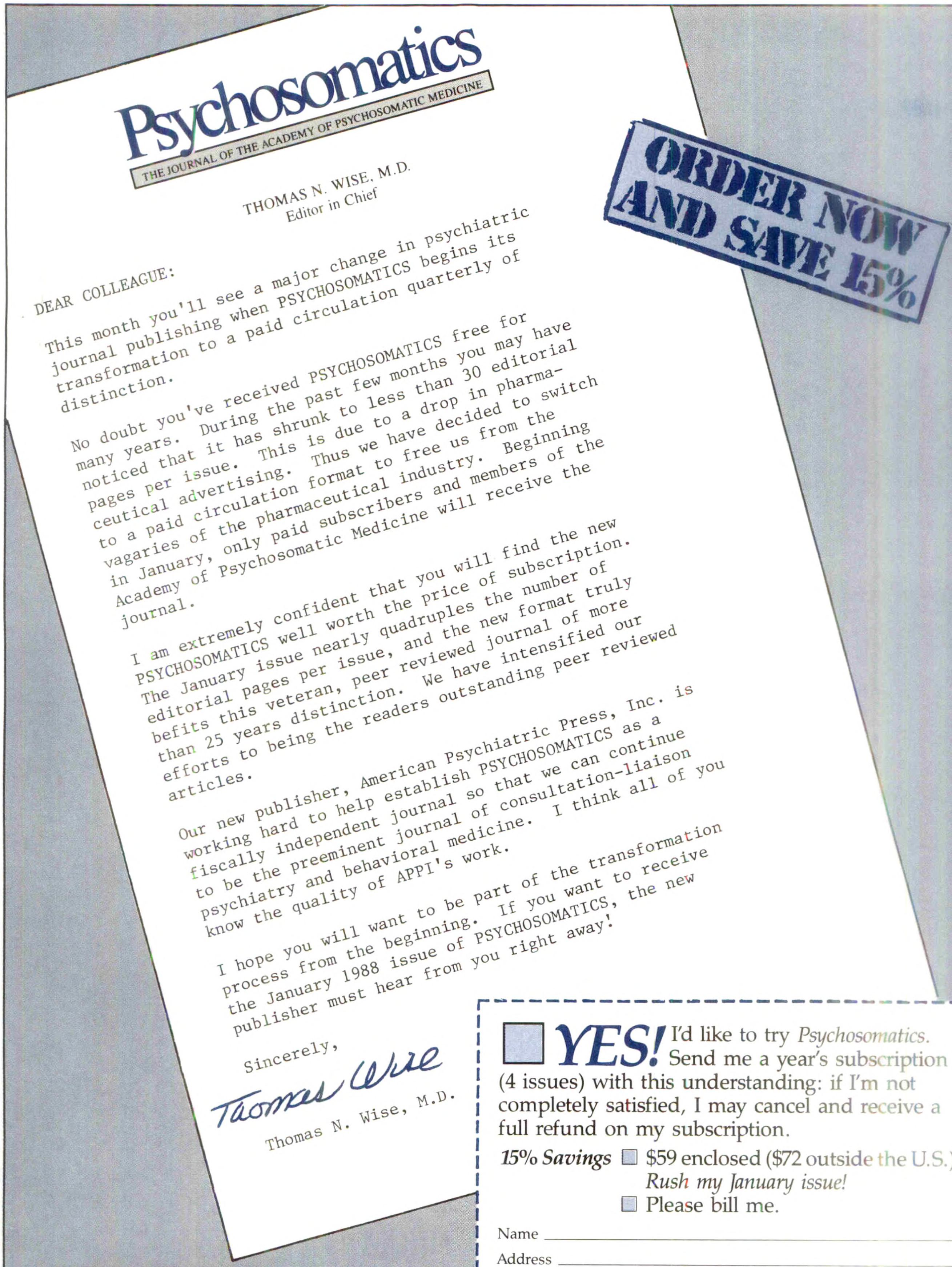

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

MARCH

March 3–5, annual meeting, American Psychopathological Association, New York. Contact Lee Robins, Ph.D., President, 4940 Audubon Ave., St. Louis, MO 63110.

March 3–5, annual meeting, Society of Professors of Child Psychiatry, Scottsdale, Ariz. Contact Joseph Green, M.D., President, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-966-7300.

March 3–6, annual meeting, American College of Physicians, New York. Contact John Ball, M.D., J.D., Executive Vice-President, 4200 Pine St., Philadelphia, PA 19104; 215-243-1200.

March 4–8, 6th World Congress of the World Association for Dynamic Psychiatry and XIX International Symposium of the German Academy for Psychoanalysis, Munich, Germany. Contact Lehr-und Forschungsinstitut für Dynamische Psychiatrie und Gruppendynamik, Wielandstr. 27/28, 1000 Berlin 15, Berlin-West, FRG; 030-881-80-50.

March 6–8, part II examinations, American Board of Psychiatry and Neurology, San Francisco. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

March 9–12, annual meeting, Association for Academic Psychiatry, Tampa, Fla. Contact Mary O'Loughlin, Dept. of Psychiatry, Mount Auburn Hospital, Cambridge, MA 02238; 617-492-3500, ext. 4309.

March 9–12, Sixth Annual Symposium in Forensic Psychiatry, American College of Forensic Psychiatry, Palm Springs, Calif. Contact Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0236.

March 14–19, annual meeting, American Society of Clinical Hypnosis, Chicago. Contact William F. Hoffmann, Jr., Executive Vice-President, 2250 East Devon Ave., Suite 336, Des Plaines, IL 60018; 312-297-3317.

March 17, annual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

March 20–22, Second International Egyptian Congress on Psychiatry, Cairo. Contact Prof. Farouk Lotaief, Secretary General of the Congress, 1A-26 July St., Apt. 801, Cairo, Egypt; 935-837.

March 20–23, annual meeting, American Association for Counseling and Development, Chicago. Contact Patrick J. McDonough, Ed.D., Executive Director, 5999 Stevenson Ave., Alexandria, VA 22304; 703-823-9800.

March 20–23, annual meeting, American College of Mental Health Administration, Woodstock, Vt. Contact Peg Pearson, Administrative Assistant, P.O. Box 66, White River Junction, VT 05001; 802-295-9363, ext. 591.

March 24–25, Fourth National Traumatic Brain Injury Symposium, Maryland Institute for Emergency Medical Services Systems, Baltimore. Contact Roberta Schwartz, M.Ed., CCC/SLP, Director, Speech-Communication Disorders Program, MIEMSS, 22 S. Greene St., Baltimore, MD 21201; 301-328-6101.

March 24–26, annual meeting, American Psychosomatic Society, Inc., Toronto. Contact George K. Degnon, Executive Director, 1311A Dolley Madison Blvd., McLean, VA 22101; 703-556-9222.

March 25–27, annual meeting, Association for Child Psychoanalysis, New Orleans. Contact Robert L. Tyson, M.D., President, 6901 Meade St., Pittsburgh, PA 15208; 412-363-0636.

March 27–31, annual meeting, American Orthopsychiatric Association, San Francisco. Contact ORTHO, 19 West 44th St., Suite 1616, New York, NY 10036; 212-354-5770.

March 28-31, 1st International Congress, The Current Status of Treatment in Child and Adolescent Psychiatry—An Update for Clinical Practice, Vienna. Contact Congress Team International (UK) Ltd., 30 Deane Way, Ruislip, Middlesex, HA4 8SX, England; 01-206-0426; Telex 923062.

March 30–April 2, annual meeting, National Council of Community Mental Health Centers, Boston. Contact Frank H. Bailey, Executive Director, 6101 Montrose Rd., Suite 360, Rockville, MD 20852; 301-984-6200.

APRIL

April 6–8, 29th National Student Research Forum, University of Texas Medical Branch, Galveston, Tex. Contact National Student Research Forum, P.O. Box 54–Station 1, UTMB, Galveston, TX 77550; 409-761-3762.

(Continued on page A36)

When the elderly patient is taking an antidepressant, there's a chance she could end up breaking a hip.

With its low incidence of orthostatic hypotension, PAMELOR lets patients stand up with less fear of falling down.[1-5]

As you know, such falls can lead to fractures, an especially serious concern for older patients. So it's important to note that, with PAMELOR, orthostatic hypotension is relatively infrequent.[1-5] In fact, in one study, patients who stopped imipramine treatment because of repeated falls experienced no such problem when switched to PAMELOR.[3]

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As with all antidepressants, patients with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary retention. PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly.

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(nortriptyline HCl)
The active metabolite of amitriptyline

For Brief Summary, please see following page.

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The active metabolite of amitriptyline

10 mg/ml 10 mg 25 mg 50 mg 75 mg

All the efficacy of amitriptyline[6] and

- low incidence of anticholinergic side effects[1,2]
- little daytime sedation[1,2,7]
- low incidence of orthostatic hypotension[1-5]

References: 1. Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. **2.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **3.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. **4.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **5.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. **6.** Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. **7.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone-marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z13—7/15/86]

PAM-1087-11

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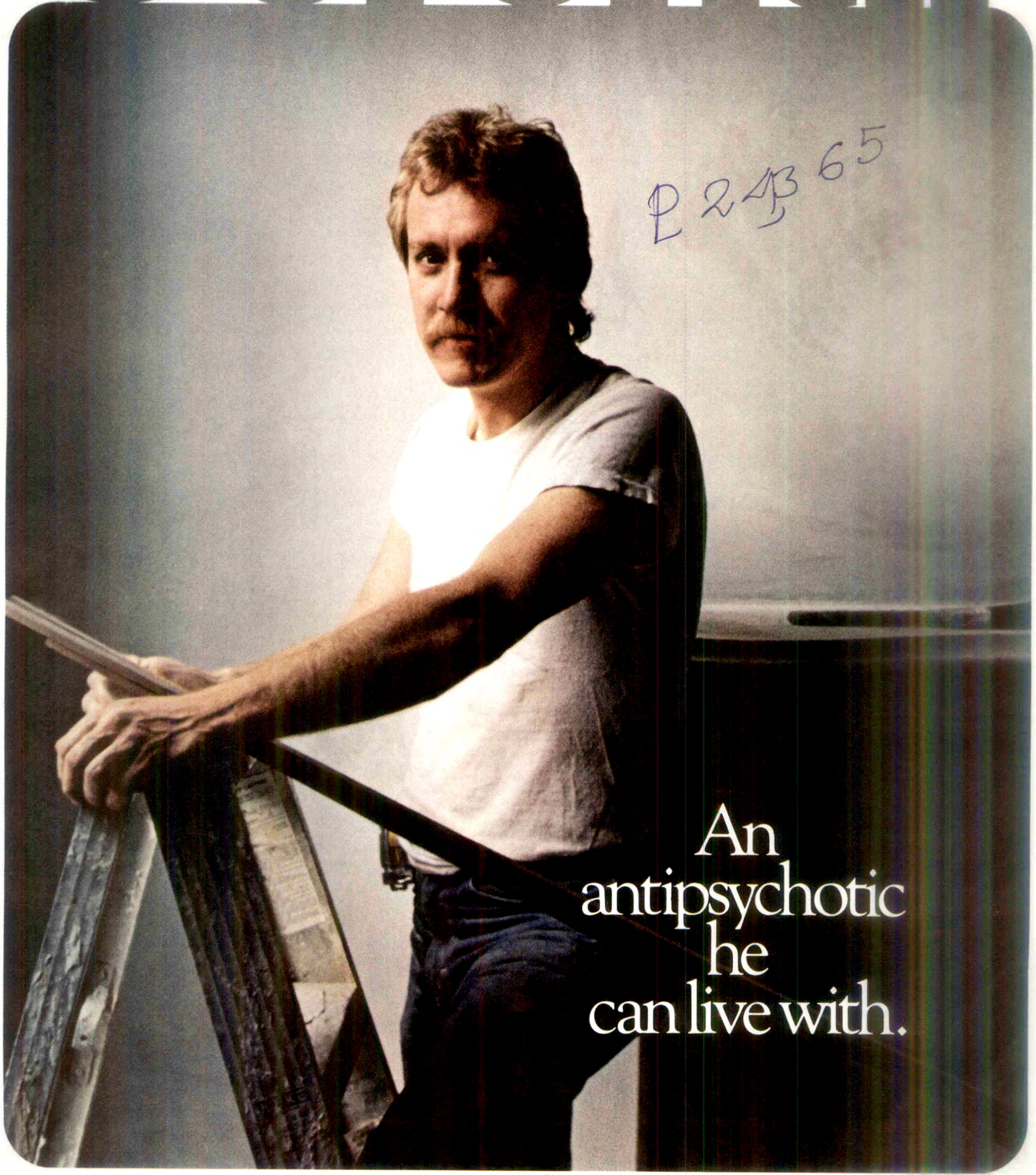

P 24365

Please see following page for brief summary of prescribing information.

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(mesoridazine) besylate oral solution USP

Tablets: 10, 25, 50 and 100 mg

Concentrate:

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions).

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse
reactions when compared with other phenothiazı
Central Nervous System: Drowsiness, Parkinson's
restlessness, ataxia, dystonia, rigidity, slurring, a
have been reported.
Autonomic Nervous System: Dry mouth, nausea
photophobia, constipation and blurred vision ha
Genitourinary System: Inhibition of ejaculation, in
been reported.
Skin: Itching, rash, hypertrophic papillae of the t
been reported.
Cardiovascular System: Hypotension and tachyc
have occurred in some instances (see Phenothia
Phenothiazine Derivatives: It should be noted t
effects have varied with the different phenothiazi
the following have occurred with one or more ph
whenever one of these drugs is used:
Autonomic Reactions: Miosis, obstipation, anore
Cutaneous Reactions: Erythema, exfoliative der
Blood Dyscrasias: Agranulocytosis, leukopenia,
aplastic anemia, pancytopenia.
Allergic Reactions: Fever, laryngeal edema, angi
Hepatotoxicity: Jaundice, biliary stasis.
Cardiovascular Effects: Changes in the terminal
including prolongation of the Q-T interval, loweri
the T wave and appearance of a wave tentativel
a U wave have been observed in some patients
including Serentil® (mesoridazine). To date, thes
repolarization and not related to myocardial dam
there is no evidence at present that these chang
significant disturbance of cardiac rhythm, it sho
unexpected deaths apparently due to cardiac a
showing characteristic electrocardiographic cha
periodic electrocardiograms has been propose
value as a predictive device. Hypotension, rarel
noted.
Extrapyramidal Symptoms: Akathisia, agitation,
trismus, torticollis, opisthotonos, oculogyric cris
Tardive Dyskinesia: Chronic use of neuroleptics
ment of tardive dyskinesia. The salient features
the **Warnings** section and below.
The syndrome is characterized by involuntary c
involve the tongue, face, mouth, lips, or jaw (e.g
cheeks, puckering of the mouth, chewing move
of the syndrome and the degree of impairment
The syndrome may become clinically recogniza
reduction, or upon withdrawal of treatment. Mov
may disappear altogether if further treatment wi
believed that reversibility is more likely after sho
exposure. Consequently, early detection of tardi
the likelihood of detecting the syndrome at the e
neuroleptic drug should be reduced periodicall
observed for signs of the disorder. This maneuv
mask the signs of the syndrome.
Endocrine Disturbances: Menstrual irregularities
weight gain, edema. False positive pregnancy t
Urinary Disturbances: Retention, incontinence.
Others: Hyperpyrexia. Behavioral effects sugge
reported. These include excitement, bizarre dre
confusional states. More recently, a peculiar ski
a side effect following long-term treatment with
by progressive pigmentation of areas of the skin
discoloration of the exposed sclera and cornea.
described as irregular or stellate in shape have
erythematosus-like syndrome.

How Supplied:
Serentil® Tablets, for oral administration: 10 mg,
(as the besylate). Bottles of 100.
Serentil® Ampuls, for intramuscular administrati
besylate)). Boxes of 20 and 100.
Serentil® Concentrate, for oral administration: C
besylate) per ml, alcohol, USP, 0.61% by volum
Immediate containers: Amber glass bottles of 4
bottles, with an accompanying dropper gradua
mesoridazine (as the besylate).

Consult package insert before prescribing.

Boehringer Ingelheim®

Boehringer Ingelhe
Pharmaceuticals, In
Ridgefield, CT 0687

DEPRESSION?

The Answer May Be On The Tip Of Your Tongue

CORTITEST™

The Saliva Depression Test

Is it depression or a medical disorder? PDLA's CORTITEST™ can help you make the determination.

The Dexamethasone Suppression Test (DST) is a widely applied laboratory determination used as a state marker for endogenous depression and objective predictor of treatment response. The test requires at least two post-dexamethasone blood draws for cortisol analysis. PDLA's CORTITEST™ eliminates the need to draw blood samples.

- Save time and money
- Convenient sample collection
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- Excellent correlation
- Children or adolescents
- Difficult patients

For additional information, please return the coupon below or telephone: **1-800-237-PDLA.**

PDLA® A Division of Psychiatric BioScience Inc.

* *Contact PDLA for clinical references regarding measuring cortisol in saliva.*

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Title ____________________ Hospital ____________________

Address ____________________

City ____________________ State ____________________ Zip ____________________

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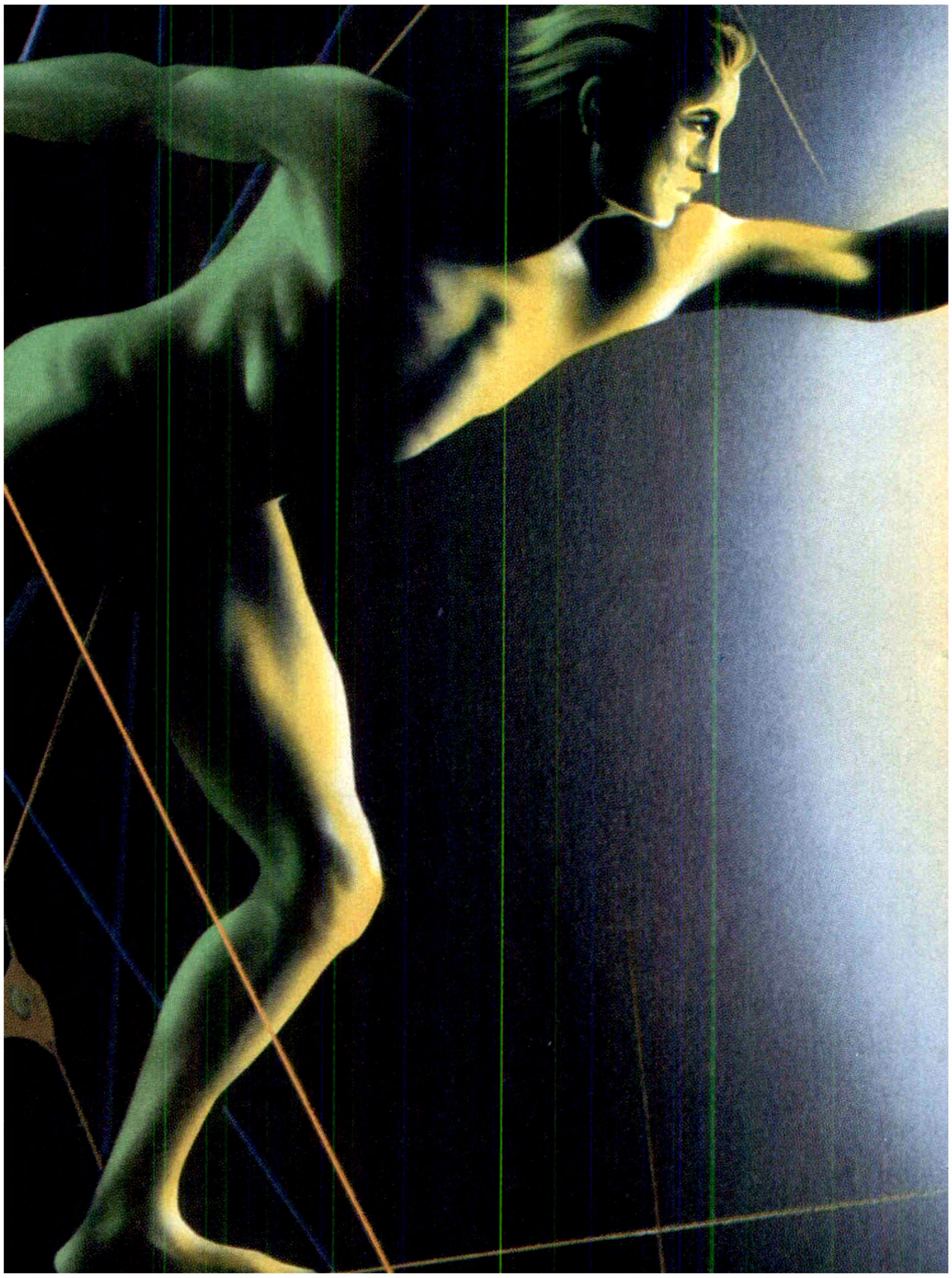
100 Corporate Court, South Plainfield, New Jersey 07080



Break free of extrapyramidal side effects with SYMMETREL®

100 MG CAPSULES
50 MG/5 ML SYRUP
(AMANTADINE HCl)

Effective control

☐ Proven control of a broad range of extrapyramidal movement disorders, including akathisia, dystonic and parkinsonian reactions[1]

Fewer side effects than anticholinergics may encourage compliance with neuroleptic therapy

☐ Unlike anticholinergics, SYMMETREL is not associated with memory impairment[2]

☐ Fewer atropine-like side effects than anticholinergics for greater patient comfort

☐ Available in capsules and a raspberry-flavored syrup

Please see following page for brief summary of prescribing information.
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Du Pont Pharmaceuticals

DU PONT
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SYMMETREL® is available exclusively from Du Pont.

SYMMETREL®

100 MG CAPSULES
50 MG/5 ML SYRUP
(AMANTADINE HCl)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATION: Drug-induced Extrapyramidal Reactions: SYMMETREL (amantadine hydrochloride) is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with the anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The adverse reactions reported most frequently (5—10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1– 5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1– 1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

Bottles of 100	NDC 0056-0105-70
Bottles of 500	NDC 0056-0105-85
Hospital Unit-Dose Blister Package of 100	NDC 0056-0105-75

As a syrup (each 5 ml [1 teaspoonful] contains 50 mg amantadine hydrochloride) in:

16 oz. (480 ml) bottles	NDC 0056-0205-16

Store at controlled room temperature (59°—86°F, 15°—30°C).

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702 and Banner Gelatin Products Corp., Chatsworth, California 91311, for Du Pont Pharmaceuticals.

References:
1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: amantadine versus benztropine. *World J Psychosynthesis* (special issue) 1984-1985; 16:40-43. **2.** McEvoy JP, McCue M, Spring B, et al: Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry* 1987; 144(5):573-577.

* D.F. Casey, *N. Engl. J. Med.* 298:516. 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

Du Pont Pharmaceuticals
E.I. du Pont de Nemours & Co. (Inc.)
Wilmington, Delaware 19898

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6043-18BSP/Rev. November 1987

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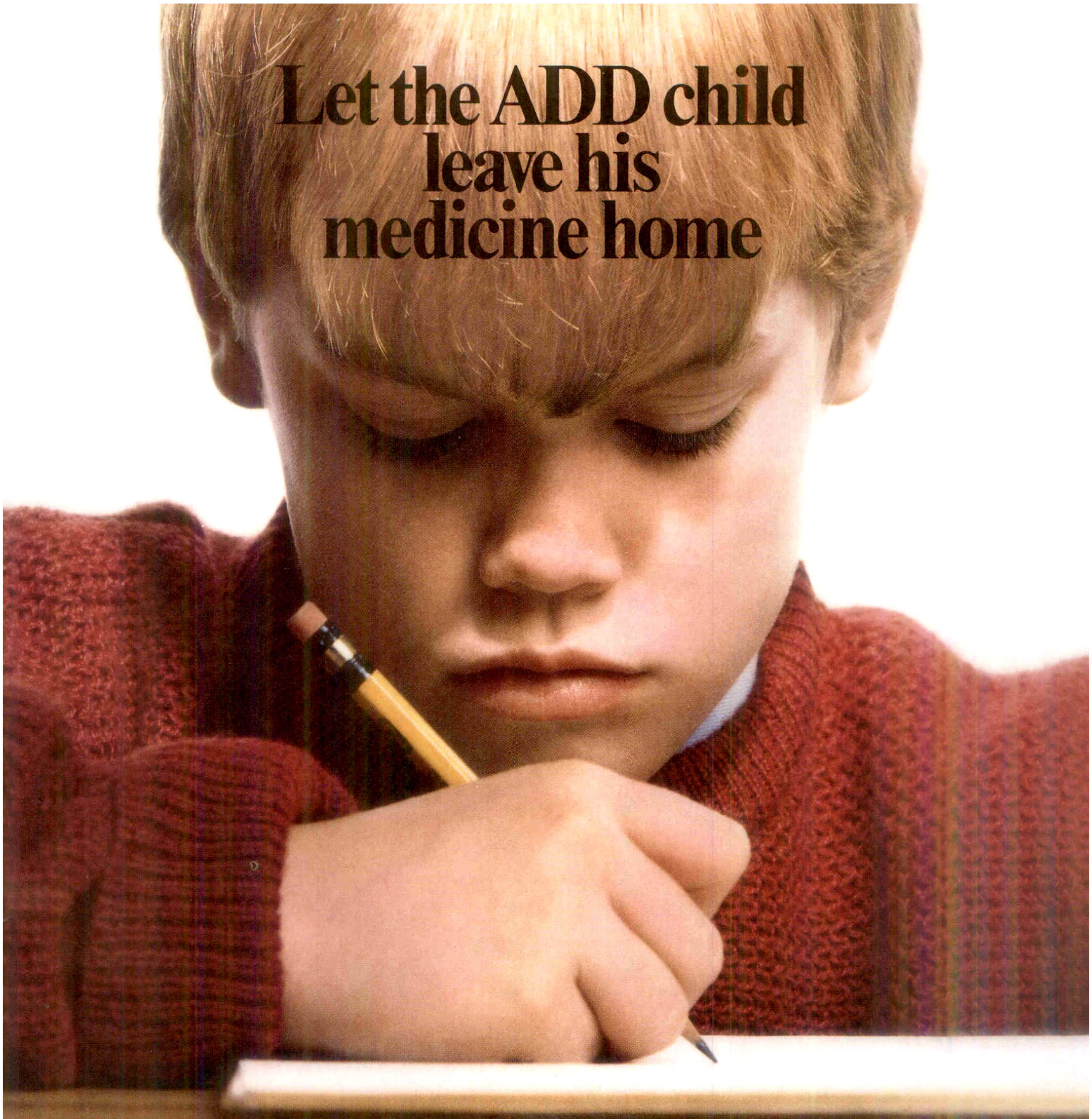


Let the ADD child leave his medicine home

Avoid the problems associated with noon dosing. One 20-mg Ritalin-SR^C tablet taken at breakfast provides a therapeutic effect equivalent to a standard 10-mg tablet taken twice a day.[1]

Also available: Regular tablets of 5 mg, 10 mg and 20 mg.

Greater convenience

No medicating at school

Teacher and school nurse not involved

Before prescribing, please consult Brief Summary of Prescribing Information on following page.

Ritalin is indicated as adjunctive therapy to other remedial measures (psychological, educational, social) for ADD children. Drug treatment is not indicated for all children with ADD. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis.

Once-a-day

RITALIN-SR® ©II

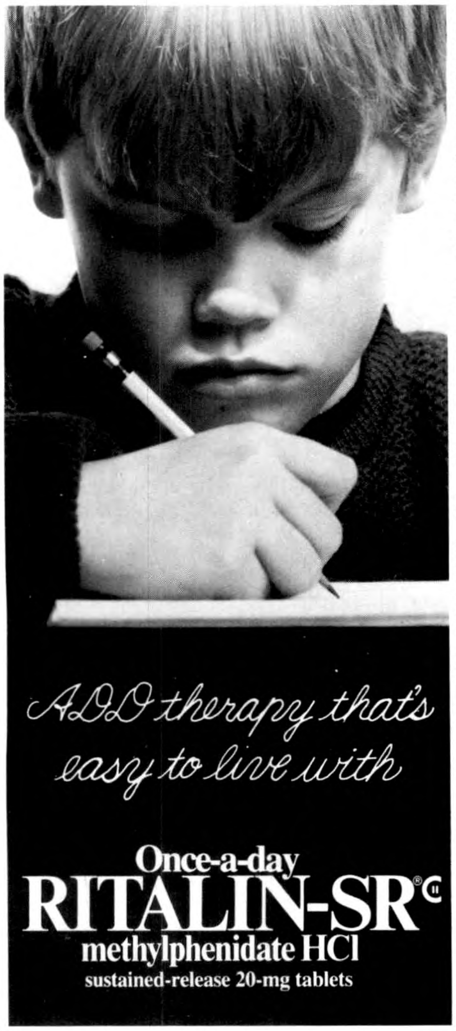
methylphenidate HCl

sustained-release 20-mg tablets

ADD therapy that's easy to live with

174-8117-A

CIBA


ADD therapy that's easy to live with
Once-a-day
RITALIN-SR® Ⓒ II
methylphenidate HCl
sustained-release 20-mg tablets

Ritalin® hydrochloride Ⓒ II
methylphenidate hydrochloride tablets USP

Ritalin-SR® Ⓒ II
methylphenidate hydrochloride USP sustained-release tablets

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Ritalin overdosage has not been established.

HOW SUPPLIED

Tablets 5 mg — round, yellow (imprinted CIBA 7)	
Bottles of 100	NDC 0083-0007-30
Bottles of 500	NDC 0083-0007-35
Bottles of 1000	NDC 0083-0007-40
Tablets 10 mg — round, pale green, scored (imprinted CIBA 3)	
Bottles of 100	NDC 0083-0003-30
Bottles of 500	NDC 0083-0003-35
Bottles of 1000	NDC 0083-0003-40
Accu-Pak® Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0083-0003-32
Tablets 20 mg — round, pale yellow, scored (imprinted CIBA 34)	
Bottles of 100	NDC 0083-0034-30
Bottles of 1000	NDC 0083-0034-40
Protect from light.	
Dispense in tight, light-resistant container (USP).	
SR Tablets 20 mg — round, white, coated (imprinted CIBA 16)	
Bottles of 100	NDC 0083-0016-30

Note: SR Tablets are color-additive free.

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight, light-resistant container (USP).

C85-55 (Rev. 11/85)

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

1. Whitehouse D, et al: Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *J Clin Psychiatry* 1980;41:282-285.

C I B A

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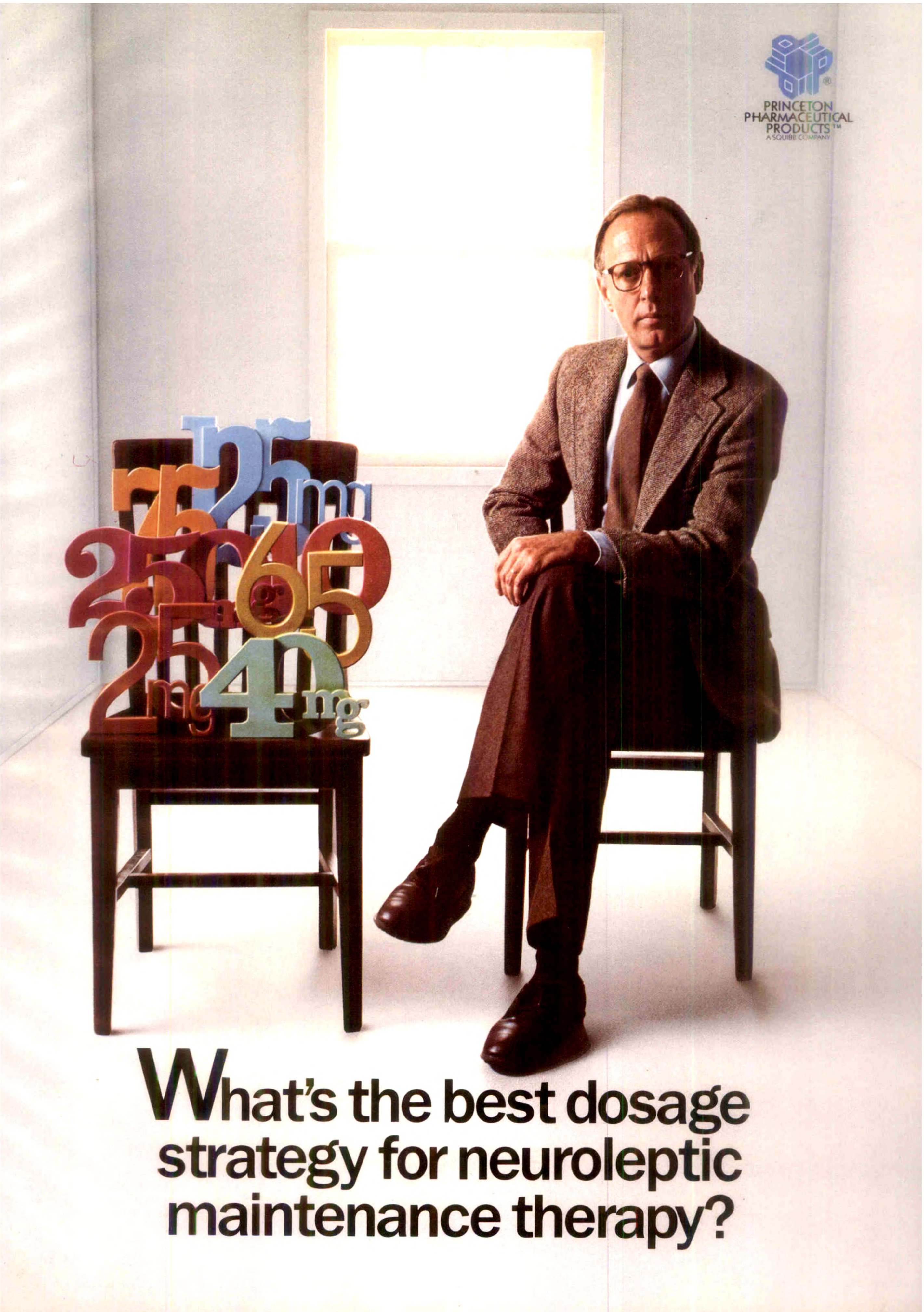
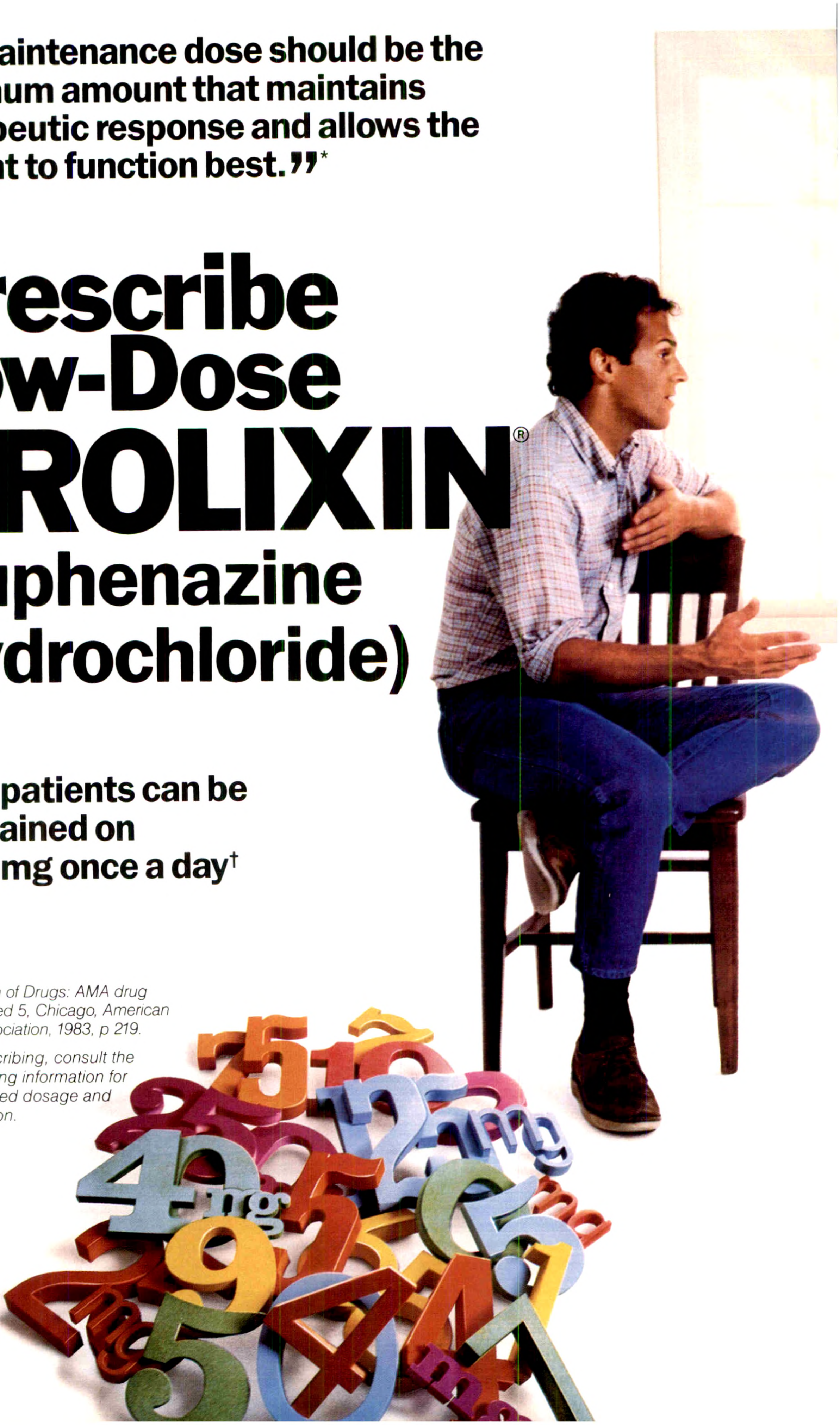


What's the best dosage strategy for neuroleptic maintenance therapy?

“The maintenance dose should be the minimum amount that maintains therapeutic response and allows the patient to function best.”*

Prescribe Low-Dose PROLIXIN®
(fluphenazine hydrochloride)



Many patients can be maintained on 1 to 5 mg once a day†

**AMA Division of Drugs: AMA drug evaluations, ed 5, Chicago, American Medical Association, 1983, p 219.*

†Before prescribing, consult the full prescribing information for recommended dosage and administration.

Safe, effective treatment

Helps avoid side effects most commonly associated with low-potency neuroleptics*

- ▶ Less sedation[1]
- ▶ Fewer anticholinergic effects[2]
- ▶ Less risk of cardiovascular effects[2]
- ▶ Rarely reported sexual dysfunction[2]

Acute care through maintenance therapy

The low-dose PROLIXIN® family of products offers continuity of care, with a dosage form for every need:

- ▶ Oral concentrate or fast-acting injection for treatment of acute psychosis
- ▶ Tablets, oral concentrate, or elixir for oral maintenance
- ▶ Long-acting PROLIXIN DECANOATE® (fluphenazine decanoate injection) for depot maintenance

Low-Dose

PROLIXIN®

(fluphenazine hydrochloride)

ORAL MAINTENANCE

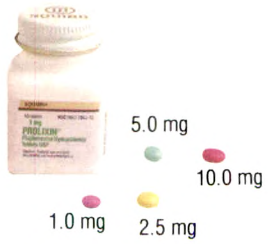
Lowering the dose, lowering dose-related side effects

* *While the risk of extrapyramidal symptoms is increased with high-potency neuroleptics, these symptoms are usually dose-related and can generally be controlled by dosage adjustments.*

Please see brief summary on last page of this advertisement.

Low-dose PROLIXIN® (fluphenazine hydrochloride)

Choose experience: Dispense as written*



PROLIXIN® Tablets

(fluphenazine hydrochloride tablets USP)

1, 2.5, 5, and 10 mg—bottles of 50 and 500, and Unimatic® unit-dose packs of 100

PROLIXIN® Oral Concentrate

(fluphenazine hydrochloride oral solution)

5 mg/mL in bottles of 120 mL with calibrated dropper

PROLIXIN® Elixir

(fluphenazine hydrochloride elixir USP)

0.5 mg/mL—orange-flavored—in bottles of 473 mL (1 pint) and 60 mL dropper-assembly bottles

PROLIXIN® Injection

(fluphenazine hydrochloride injection USP)

2.5 mg/mL in multiple-dose vials of 10 mL

*Please check the substitution laws in your state.

PROLIXIN®
Fluphenazine Hydrochloride
INJECTION/TABLETS/ELIXIR/ORAL CONCENTRATE
PROLIXIN DECANOATE®
Fluphenazine Decanoate Injection

DESCRIPTION: PROLIXIN Injection (Fluphenazine Hydrochloride Injection USP), **FOR INTRAMUSCULAR USE ONLY,** provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) provide 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. PROLIXIN 2.5, 5, and 10 mg tablets contain FD&C Yellow No. 5 (tartrazine). PROLIXIN Elixir (Fluphenazine Hydrochloride Elixir USP) provides 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. PROLIXIN Oral Concentrate (Fluphenazine Hydrochloride Oral Solution) provides 5 mg fluphenazine hydrochloride per mL, with 14% alcohol by volume. PROLIXIN Decanoate (Fluphenazine Decanoate Injection) provides 25 mg fluphenazine decanoate per mL in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as preservative.

CONTRAINDICATIONS: In the presence of suspected or established subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur. Fluphenazine Decanoate is not intended for use in children under 12.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative effective, less harmful treatments are *not* available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)

This potentially fatal symptom complex has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnostic evaluation is complicated; it is important to identify both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

Management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. Carefully consider the potential reintroduction of drug therapy in patients requiring antipsychotic drug treatment after recovery from NMS since recurrences have been reported. Such patients should be monitored.

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Severe adverse reactions requiring immediate medical attention may possibly occur. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine. "Silent pneumonias" are possible. Fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

ADVERSE REACTIONS: *Central Nervous System:* Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. One can expect a higher incidence of such reactions with fluphenazine decanoate than with less potent piperazine derivatives or straight-chain phenothiazines. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

References: 1. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc , 1980, p 415. **2.** Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 203, 221, 239.

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Please see brief summary continuing on following page.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue protrusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

Other CNS Effects: Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occur, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea, loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines. Local tissue reactions occur only rarely with injections of fluphenazine decanoate.

HOW SUPPLIED: *Injection*—in multiple-dose vials of 10 mL. *Tablets*—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100 and 500, and in Unimatic® cartons of 100. *Elixir*—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated dropper. *Oral Concentrate*—in bottles of 120 mL with calibrated dropper. *Fluphenazine Decanoate*—in 1 mL Unimatic® single dose preassembled syringes and 5 mL vials.

For full prescribing information, consult package inserts. (J4-153A/120B/147B/150A)

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(Continued from page A20)

April 13–16, annual meeting, National Council on the Aging, Inc., Washington, D.C. Contact Ruth Blank, Conference and Special Events, 600 Maryland Ave., S.W., West Wing 100, Washington, DC 20024; 202-479-1200.

April 13–17, annual meeting, American Association of Suicidology, Washington, D.C. Contact Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

April 14–16, annual meeting, Group for the Advancement of Psychiatry, White Plains, N.Y. Contact Jerry M. Lewis, M.D., President, P.O. Box 330, Greenbelt, MD 20770; 301-345-8030.

April 16, annual meeting, Bulimia Anorexia Self-Help, Inc., St. Louis. Contact Felix E.F. Larocca, M.D., President, 6125 Clayton Ave., Suite 215, St. Louis, MO 63139; 314-567-4080.

April 17–20, annual meeting, American Occupational Therapy Association, Phoenix, Ariz. Contact Executive Director, 1383 Piccard Dr., Rockville, MD 20850; 301-948-9626.

April 17–23, annual meeting, American Academy of Neurology, Cincinnati. Contact AAN, 2221 University Ave., S.E., Suite 335, Minneapolis, MN 55414; 612-623-8115.

April 21–24, 19th Annual Medical-Scientific Conference, American Medical Society on Alcoholism & Other Drug Dependencies, Washington, D.C. Contact Claire Osman, AMSAODD Administrative Director, 12 West 21st St., New York, NY 10010; 212-206-6770.

April 21–25, annual meeting, National Council on Alcoholism, Inc., Washington, D.C. Contact Thomas V. Seesel, Executive Director, 12 West 21st St., 7th Fl., New York, NY 10010; 212-206-6770.

April 23–29, annual meeting, American Occupational Medical Association, New Orleans. Contact Donald L. Hoops, Ph.D., Executive Director, 2340 S. Arlington Heights Rd., Suite 400, Arlington Heights, IL 60005; 312-228-6850.

April 26–30, annual meeting, Society of Behavioral Medicine, Boston. Contact Judith C. Woodward, Executive Director, P.O. Box 8530, Knoxville, TN 37996; 615-974-5164.

April 27–May 1, annual meeting, American Association of Sex Educators, Counselors and Therapists, San Francisco. Contact Ruth Hunt, Ph.D., Executive Director, 11 Dupont Circle, N.W., Suite 220, Washington, DC 20036; 202-462-1171.

April 28–30, First International Congress Asian/Pacific Region, Reflections on Mental Health, Sydney, Australia. Contact Congress Secretariat, P.O. Box 11, Torrens, Canberra, 2607, Australia; 062-86-1588.

April 28–May 1, annual meeting, American Association of Pastoral Counselors, Portland, Ore. Contact James W. Ewing, Ph.D., Executive Director, 9508 A Lee Hwy., Fairfax, VA 22031; 703-385-6967.

MAY

May 1–4, semiannual meeting, World Psychiatric Association, Sydney, Australia. Contact Fini M. Schulsinger, Secretary General, Kommunehospitalet, DK-1399 Copenhagen K, Denmark; 45-1-938500, ext. 3390.

May 2–6, annual meeting, American Pediatric Society, Washington, D.C. Contact Audrey Brown, M.D., Secretary-Treasurer, 450 Clarkson Ave., Brooklyn, NY 11203; 718-270-1692.

May 2–6, IV International Congress on Rehabilitation in Psychiatry, Orebro, Sweden. Contact S. Rost, M.D., Psychiatric Rehabilitation Dept., Regional Hospital, 700 04 Orebro 4, Sweden; 019-15-31-01.

May 4–6, annual meeting, Canadian College of Neuropsychopharmacology, Montreal. Contact Dr. P. Boska, Douglas Hospital Research Centre, 6875 LaSalle Blvd., Verdun, Quebec, Canada H4H 1R3; 514-761-6131.

May 4–7, annual meeting, American Association for the History of Medicine, Inc., New Orleans. Contact Edward C. Atwater, M.D., Secretary-Treasurer, 601 Elmwood Ave., Rochester, NY 14642; 716-275-2903.

May 4–7, annual meeting, Royal Australian and New Zealand College of Psychiatrists, Sydney, Australia. Contact Peter H. Carter, Registrar, 101 Rathdowne St., Carlton, Victoria, Australia 3053; 03-6635466.

May 4–8, annual meeting, American Psychoanalytic Association, Montreal. Contact Helen Fischer, Administrative Director, 309 East 49th St., New York, NY 10017; 212-752-0450.

May 5–8, annual meeting, American Academy of Psychoanalysis, Montreal. Contact Vivian Mendelsohn, Executive Director, 30 East 40th St., Suite 608, New York, NY 10016; 212-675-4105.

May 5–8, annual meeting, American Society of Group Psychotherapy and Psychodrama, San Diego. Contact Stephen F. Wilson, A.C.S.W., Executive Director, 116 East 27th St., New York, NY 10016; 212-725-0046.

May 7, annual meeting, American College of Psychoanalysts, Montreal. Contact Alex H. Kaplan, M.D., Secretary General, 4524 Forest Park Ave., St. Louis, MO 63108; 314-367-6243.

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Are Psychiatric Educators "Losing the Mind"?
By Morton F. Reiser

Physicians prescribe Ativan for what it doesn't do—as well as for what it does

1

Ativan® doesn't
significantly delay clearance because of age or kidney or liver dysfunction

2

Ativan® doesn't
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3

Ativan® doesn't
have a complex metabolism—has short duration of action

4

Ativan® doesn't
have prolonged accumulation—seldom produces unwanted sedation (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

5

Ativan® doesn't
cause significant changes in vital signs in cardiovascular patients*

...it does effectively relieve anxiety

Ativan®
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See important information on following page.

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*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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- Medically necessary
- Brand necessary
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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

®

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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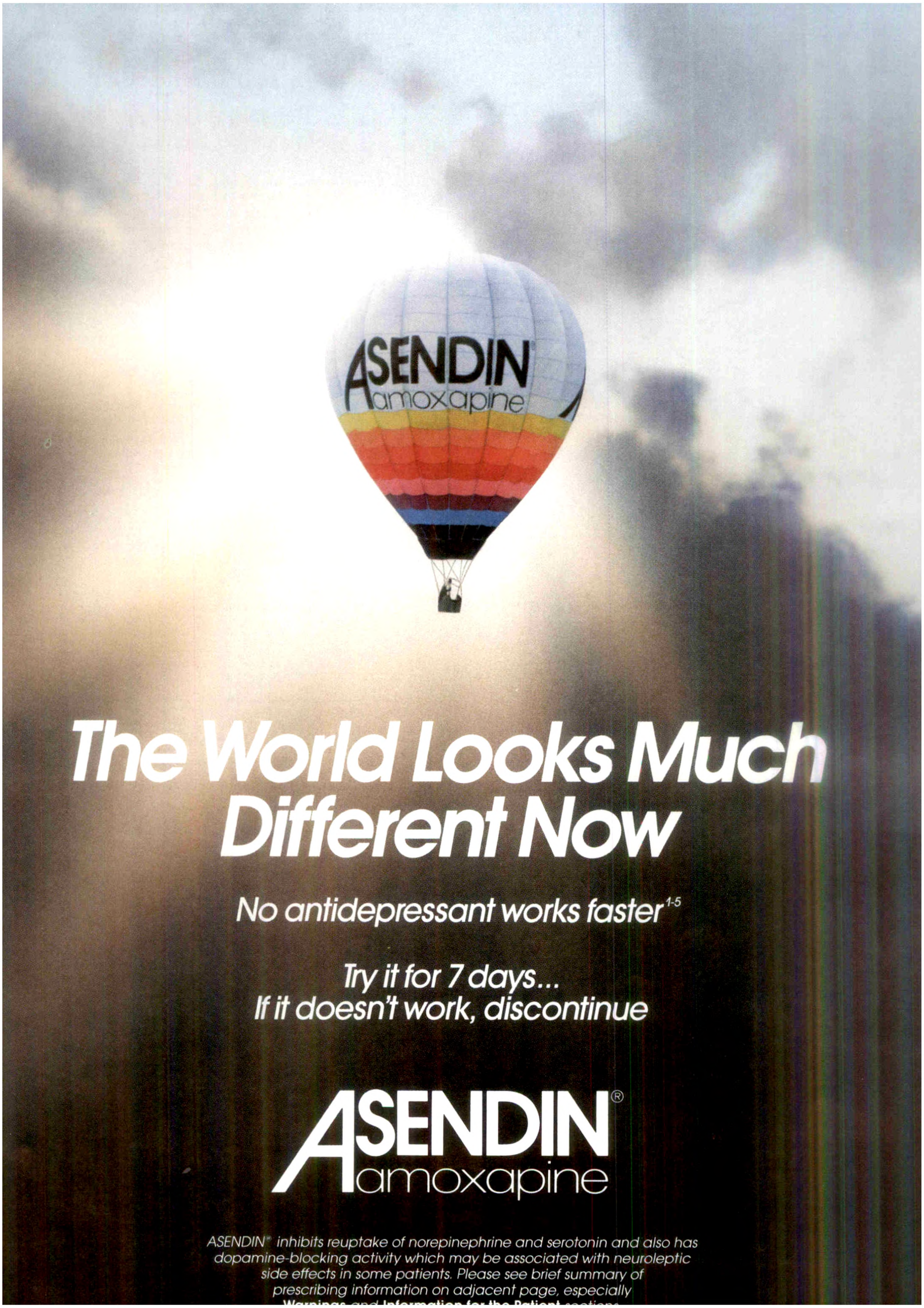
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If it doesn't work, discontinue
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ASENDIN® inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** *and* **Information for the Patient** *sections.*

ASENDIN®
amoxapine

BRIEF SUMMARY
ASENDIN® amoxapine Tablets, 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: *ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.*

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro *tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.*

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: *ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.*

CONTRAINDICATIONS: *Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN®* amoxapine, *allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.*

WARNINGS: Tardive Dyskinesia: *Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.*

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: *Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN®* amoxapine *should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.* Information for the patient: *It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired.* Drug interactions: *See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.* Therapeutic interactions: *Concurrent administration with electroshock may increase hazards associated with such therapy.* Carcinogenesis, impairment of fertility: *In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.* Pregnancy. Pregnancy Category C: *Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* Nursing mothers: *ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.* Pediatric use: *Safety and effectiveness in children below the age of 16 have not been established.*

ADVERSE REACTIONS: *Reported in Controlled Studies:* Incidence greater than 1%—*Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).*

Less frequently reported reactions were: CNS and Neuromuscular—*anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.* Allergic—*edema, skin rash.* Endocrine—*elevation of prolactin levels.* Gastrointestinal—*nausea.* Other—*dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.* Incidence less than 1%—Anticholinergic—*disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.* Cardiovascular—*hypotension, hypertension, syncope, tachycardia.* Allergic—*drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis.* CNS and Neuromuscular—*tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported.* Hematologic—*leukopenia, agranulocytosis.* Gastrointestinal—*epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.* Endocrine—*increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.* Other—*lacrimation, weight gain or loss, altered liver function.* Drug Relationship Unknown: *Reported rarely, but under circumstances where drug relationship was unknown:* Anticholinergic—*paralytic ileus.* Cardiovascular—*atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.* CNS and Neuromuscular—*hallucinations.* Hematologic—*thrombocytopenia, eosinophilia, purpura, petechiae.* Gastrointestinal—*parotid swelling.* Endocrine—*change in blood glucose levels.* Other—*pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.*

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—*sublingual adenitis, dilation of the urinary tract.* CNS and Neuromuscular—*delusions.* Gastrointestinal—*stomatitis, black tongue.* Endocrine—*gynecomastia.*

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine *overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.*

Treatment

*Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med *1982; 306: 1337-1340).*

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

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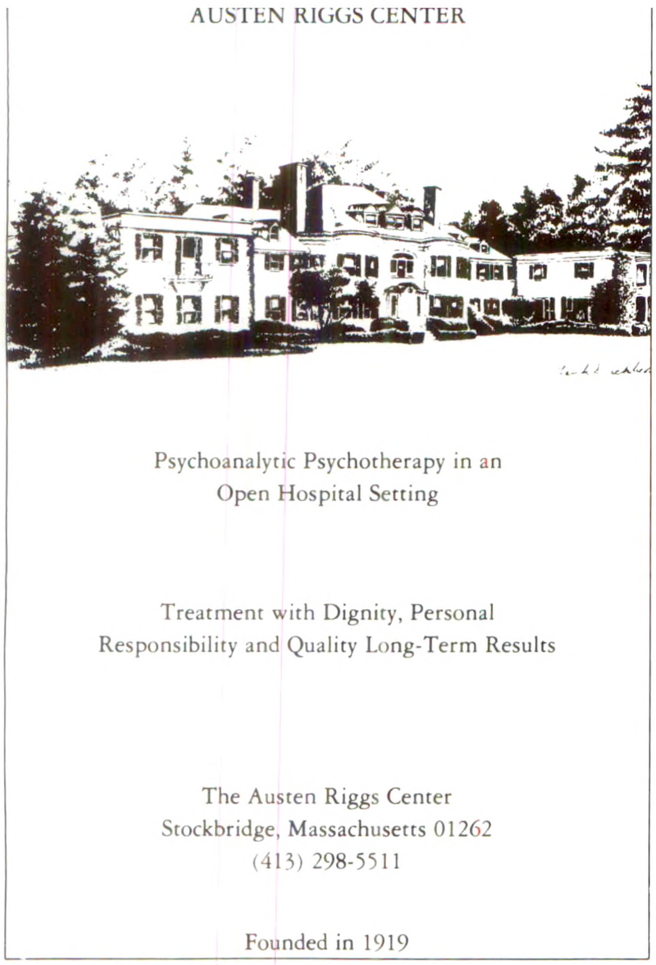

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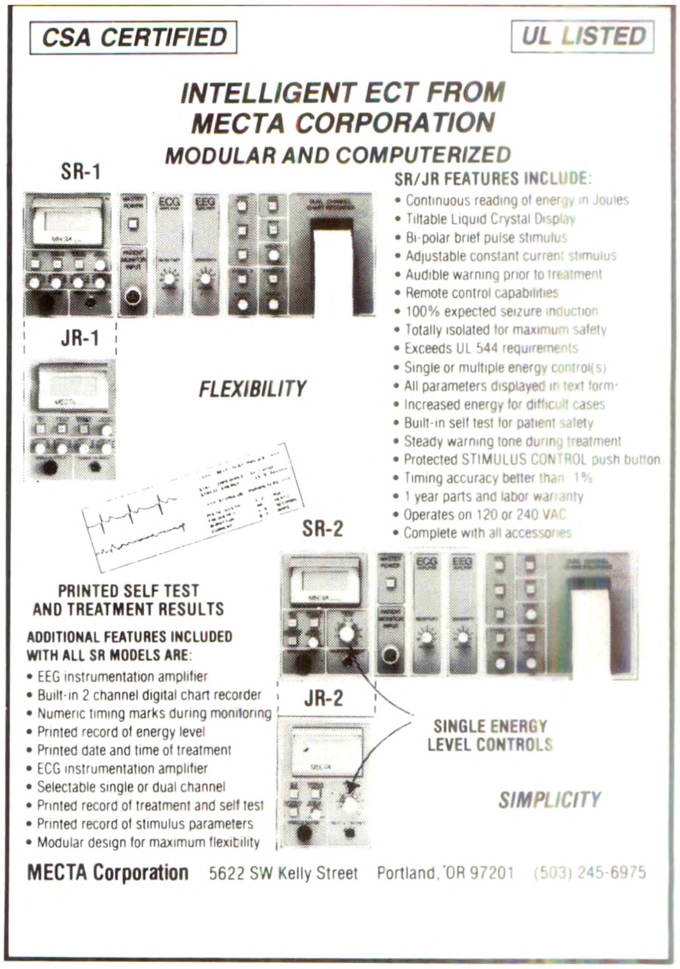

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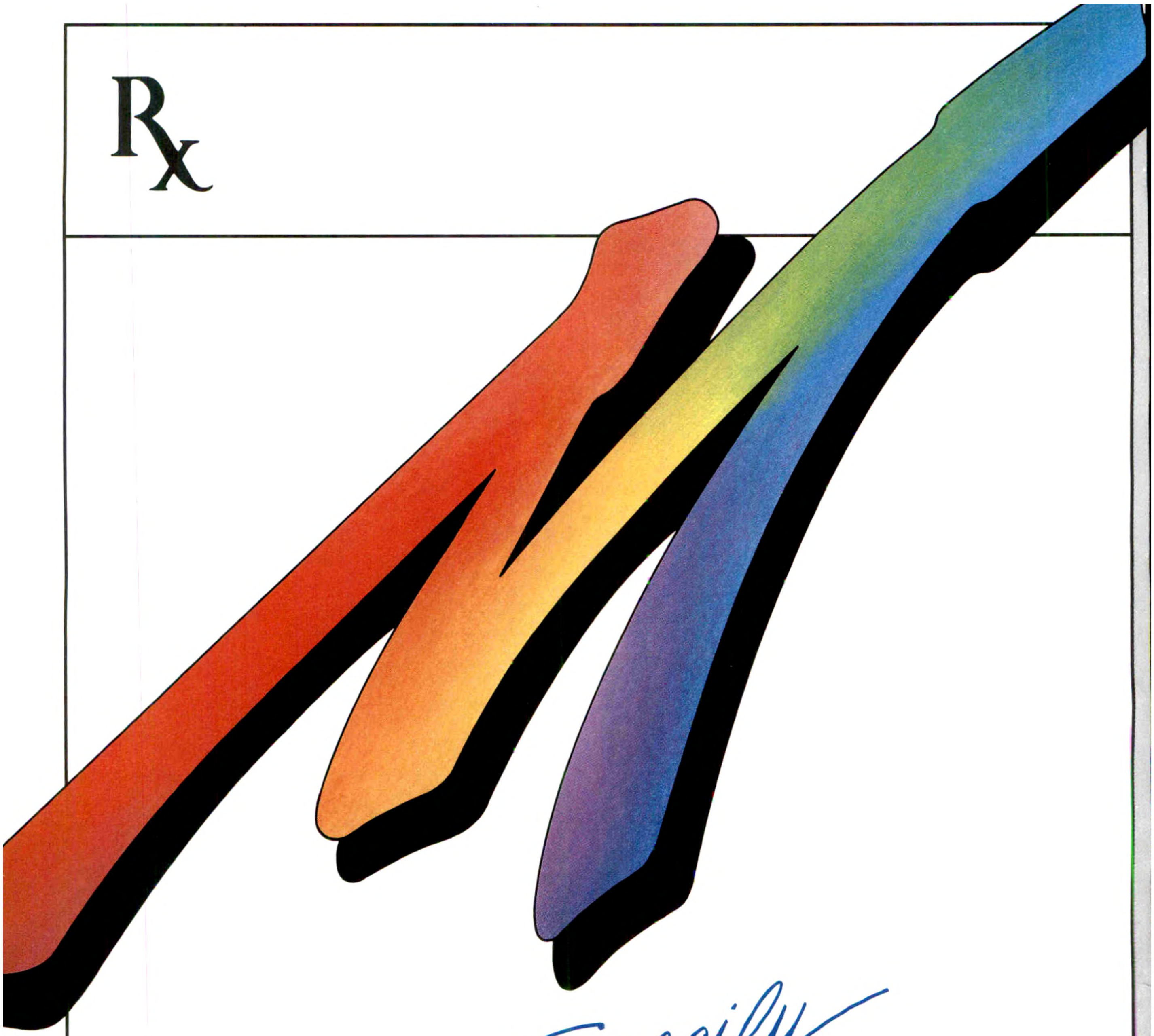

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THE AMERICAN JOURNAL OF PSYCHIATRY

Developmental Psychiatry Comes of Age

John Bowlby, M.D.

Although Meyer and Freud believed that the seeds of mental health are sown in childhood, systematic research has proved difficult and disappointing, and theory has remained intensely controversial. Research of the past two decades by developmental psychologists using an ethologically based theory of socioemotional bonds, however, is yielding findings that consistently confirm predictions. The author outlines this research, giving examples of the results, which are shown to be compatible with findings of epidemiological studies of depressed adults. He holds that a person's degree of vulnerability to stressors is strongly influenced by the development and current state of his or her intimate relationships.

(Am J Psychiatry 1988; 145:1–10)

During the first third of this century there were two great proponents of developmental psychiatry—Adolf Meyer and Sigmund Freud. Both believed that the seeds of mental health and ill health are sown in childhood and that, if we are to understand the present-day functioning of a person, it is necessary to know how he or she has become the man or woman we meet today.

In their approaches to the field, Meyer and Freud took very different routes. Initially, Freud focused on traumatic family relationships, including incest, but for reasons that remain obscure, he later claimed that the real-life events he had originally invoked as pathogenic had never occurred and that the patient had only imagined them. Thenceforward the emphasis was on fantasy. Consequently, Freud's interests became focused on a person's internal world of mental processes, especially on the powerful influence that unconscious processes have on the way a person feels, thinks, and behaves and, above all, on the defensive processes that actively keep them unconscious.

Meyer, by contrast, continued to emphasize the role of real-life events in shaping personality, but he was never very specific about the nature of the ones that matter, nor did he advance any theory of how being exposed to some event or situation affects a person's mental state. Nonetheless, Meyer's approach played a major part in promoting the mental hygiene movement and child psychiatry. In both these revolutionizing movements the notion that the environment in which a child grows up plays a critical part in determining his or her future mental health has always been a stubbornly held if ill-defined assumption. Moreover, these are the fields in which Freud's original ideas about the role of childhood trauma have not only persisted but borne valuable fruits.

We can see now that the tremendous strides being made today in developmental psychiatry owe a great deal to both these pioneers. To Adolf Meyer is due the credit for having continued to emphasize the influential role of the events and situations people meet with during their development. To Sigmund Freud is due the credit for having emphasized the influence on how people think, feel, and behave that is exerted by their internal world—namely, by the way they perceive, construe, and structure the events and situations they encounter. Today we know that the central task of developmental psychiatry is to study the endless interaction of internal and external and how the one is constantly influencing the other, not only during childhood but during adolescence and adult life as well.

Evidence that happenings within the family during childhood and adolescence play a major role in determining whether a person grows up to be mentally healthy or not is now formidable, and a review of the important epidemiological findings appeared in 1985 (1). For that reason, in this paper I will present only a limited amount of data, some epidemiological and

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Presented as the Adolf Meyer Lecture at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received Aug. 29, 1986; accepted Dec. 9, 1986. Address reprint requests to Dr. Bowlby, Tavistock Clinic, 120 Belsize Lane, London, NW3 5BA, England.

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retrospective and some ethological and prospective, and will give most attention to the conceptual framework within which I believe the different sets of findings can best be comprehended.

As an example of retrospective data I draw on the findings of the group led by George Brown and Tirril Harris, which has been undertaking sophisticated epidemiological studies to explore the roles of family experience and other social variables as antecedents of depressive and anxiety disorders in adult life. As an example of prospective data, I draw on the work of those developmental psychologists who have been inspired by and are busy expanding the brilliant pioneering studies of Mary Ainsworth. This research into the development of a young child's capacity to make intimate emotionally mediated relationships with parents is probably little known as yet among general psychiatrists. Since the findings from these two quite different approaches are highly compatible, the resulting scientific structure can be likened to a trilithon made up of two stout pillars of evidence and a crosspiece of theory. A major conclusion is that, whatever influence variations in genetic endowment may exert on personality development and psychopathology, an immense influence is unquestionably exerted by environmental variables of the kinds now being systematically explored.

EMOTIONALLY MEDIATED BONDS AND MENTAL HEALTH

For many years, sensitive clinicians have been aware that a person's mental state is deeply influenced by whether his or her intimate personal relationships are warm and harmonious or tense, angry, anxious, emotionally remote, or, possibly, nonexistent. Among clinicians so oriented a variety of terms are in use: "significant other," "dependency," "symbiosis," and "object relations." Nevertheless, although a field of manifest importance to psychiatry, there has been no agreement on how best to conceptualize it. A number of theoretical systems have been proposed, almost all of them derived in some sort of way from psychoanalysis, and a mountain of jargon has accumulated. Yet none has generated sustained productive research. In scientific quarters the whole field still struggles for recognition.

Some years ago, as a family psychiatrist researching the effects on young children of being removed from their home to the care of strange people, I was faced with a problem. Since young children in that situation are intensely distressed and show every sign that they desperately wish to recover their mother, the question arises: How do we understand the origin and nature of this extraordinarily strong tie between child and mother? The only theory extant at that time was that a child becomes emotionally linked to his mother because she feeds him. Dissatisfied with that explanation, I was lucky enough to be introduced to the ideas of Konrad Lorenz. Ethologists, I discovered, were just as interested in the strong bonds between offspring and parents in a range of animal species as I was in those of the human species. Moreover, as professional biologists, their approach was radically different from anything I had met with among psychologists and psychiatrists. Bonds between individuals, I learned, which occur in a great array of mammalian and avian species, could be studied experimentally and their survival function considered in the light of evolution theory.

Here then was a possible new approach to our problem and one that seemed to fit our data. Not only that, but the ethologists had developed sensitive means for observing and recording and were sophisticated scientists with their feet firmly planted in the biological sciences. The upshot was that I fell for this approach and decided to explore its potentials. Now, 30 years later, I am glad I embarked on the gamble. Thanks to the work of many gifted colleagues, the bare bones of theory are becoming clothed with hard-wearing empirical garments, and there are now several productive research programs studying the different ways in which intimate personal relationships can develop, with their causes and consequences. These research programs are as firmly rooted in biology as are those of the physiological psychiatrists who have improperly kidnapped the label "biological psychiatry."

Not only are ethological concepts proving extremely fruitful when applied to our field, but present-day science provides us many other concepts, not available to Meyer or Freud, that help us explain our data. For example, additional concepts of high explanatory value in our field come from control theory and cognitive psychology, including human information processing.

Among the principal propositions of this new approach (2, 3) are the following: 1) Emotionally significant bonds between individuals have basic survival functions and therefore a primary status. 2) They can be understood by postulating cybernetic systems situated within the CNS of each partner that have the effect of maintaining proximity or ready accessibility of each partner to the other. 3) In order for the systems to operate efficiently, each partner builds in his or her mind working models of self and of other and of the patterns of interaction that have developed between them. 4) Present knowledge requires that a theory of developmental pathways should replace theories that invoke specific phases of development in which it is postulated a person may become fixated and/or to which he or she may regress.

The bonds with which developmental psychiatry is principally concerned are those of child to parent and the complementary bond of parent to child. The key hypothesis is that variations in the way these bonds develop and become organized during the infancy and childhood of different individuals are major determinants of whether a person grows up to be mentally healthy. Before discussing variations, however, it is necessary to consider how the bonds themselves are best conceived.

FUNCTION AND ORGANIZATION OF EMOTIONAL BONDS

Ethological theory regards the propensity to make strong emotional bonds to particular individuals as a basic component of human nature, already present in germinal form in the neonate and continuing through adult life into old age. During infancy and childhood, bonds are with parents (or parent substitutes), who are looked to for protection, comfort, and assistance. During healthy adolescence and adult life these bonds persist but are complemented by new bonds, commonly of a heterosexual nature. Although food and sex sometimes play important roles in such relationships, the relationship exists in its own right and has an important survival function of its own—namely, protection. Thus, within the attachment framework, bonds are seen as neither subordinate to nor derivative from food and sex. Nor is the urgent desire for comfort and support in adversity regarded as childish, as dependency theory implies. Instead, the capacity to make bonds with other individuals, sometimes in the care-seeking role and sometimes in the caregiving one, is regarded as a principal feature of effective personality functioning and mental health.

As a rule, care seeking is shown by a weaker and less experienced individual toward someone regarded as stronger and/or wiser. A child or older person in the care-seeking role keeps within range of the caregiver, the degree of closeness or of ready accessibility depending on circumstances; hence, the concept of attachment behavior.

Another basic component of human nature is the urge to explore the environment, to play, and to take part in varied activities with peers. This behavior is, of course, antithetical to attachment behavior. When individuals of any age are feeling secure they are likely to explore away from their attachment figure. When alarmed, anxious, tired, or unwell they feel an urge toward proximity. Thus, we see the typical pattern of interaction between child and parent known as exploration from a secure base. Provided the parent is known to be accessible and will be responsive when called upon, a healthy child feels secure enough to explore. At first these explorations are limited both in time and space. Around the middle of the 3rd year, however, a secure child begins to become confident enough to increase time and distance away—first to half-days and later to whole days. As he or she grows into adolescence, the excursions are extended to weeks or months, but a secure home base remains indispensable nonetheless for optimal functioning and mental health. No concept within the attachment framework is more central to developmental psychiatry than that of the secure base.

An obvious way to conceptualize the behavior observed is to postulate the existence of a control system within the CNS analogous to the physiological control systems that maintain physiological measures, such as blood pressure and body temperature, within set limits. Thus, the theory proposes that, in a way analogous to physiological homeostasis, the attachment control system maintains a person's relation to his or her attachment figure between certain limits of distance and accessibility. As such, it can be regarded as an example of what can usefully be termed "environmental homeostasis" (3). Among situations that activate care seeking are anything that frightens a child or signals that he or she is tired or unwell. Among situations that terminate care seeking and release the child for other activities are comfort and reassurance. Since control systems are themselves sources of activity, traditional theories of motivation that invoke a buildup of psychic energy or drive are rendered obsolete.

Control systems, by nature, can operate effectively only within a specified environment. For example, the system regulating body temperature cannot maintain an appropriate temperature when environmental conditions become either too hot or too cold, which means that whenever conditions go beyond certain limits the whole organism becomes stressed or dies. Viewed in an evolutionary perspective, it is evident that variation and natural selection have resulted in each organism's physiological systems being so constructed that they operate effectively in the environment to which the species has become adapted and that they will become stressed or fail in others.

An evolutionary perspective is necessary also if we are to understand psychological stress and the environmental conditions that cause it. Like other control systems, the system governing human attachment behavior is constructed so as to promote survival in the environment in which man evolved. Since in such an environment it is essential for survival that an infant or older child has an attentive and responsive caregiver to whom to go in an emergency, it follows that his or her attachment system will be constructed so as to operate most efficiently in interaction with a person who the child believes will respond promptly and effectively when called upon. It is not at all surprising, therefore, that a failure in response of his or her familiar caregiver, whether due to physical absence or a failure to respond appropriately, should always cause stress and sometimes be traumatic.

This leads to consideration of the third major component of human nature relevant to this exposition—namely, caregiving, which is the prime role of parents and complementary to attachment behavior. When looked at in terms of evolution theory the occurrence of altruistic care of the young is readily understood, since it serves to promote the survival of offspring (and often of other relatives as well) and thereby the individual's own genes. Nevertheless, this form of explanation constitutes a radical shift from most psychological theorizing, including Freud's, which has mistakenly assumed that individuals are by nature essentially selfish and that they consider the interests of others only when constrained to do so by social pressures and sanctions. Nothing, I believe, that stems from an ethological perspective has more far-reaching implications for understanding human nature than this reappraisal of altruism.

It is evident that, to operate efficiently, the attachment control system within the child requires to have at its disposal as much information as possible about the self and the attachment figure, not only in regard to their respective locations and capabilities but in regard also to how each is likely to respond to the other as environmental and other conditions change. Observations lead us to conclude that toward the end of the first year of life children are acquiring considerable knowledge of their immediate world and that during subsequent years this knowledge is best regarded as becoming organized in the form of internal working models, including models of self and mother. The function of these models is to simulate happenings in the real world, thereby enabling individuals to plan their behavior with all the advantages of insight and foresight. The more adequate and accurate the simulation, of course, the better adapted is the behavior based on it likely to be (4). Although our knowledge of the rate at which these models develop during the earliest years is still scanty, there is good evidence that by their 5th birthday most children are using a sophisticated working model of mother or mother-substitute which includes knowledge of her interests, moods, and intentions, all of which the child can then take into account (5). With a complementary model of self, the child is already engaging in a complex intersubjective relationship with the mother, who, of course, has her own working models both of her child and of herself. Because these models are in constant use, day in and day out, their influence on thought, feeling, and behavior becomes routine and largely outside of awareness.

As clinicians we know that long before children reach the age of 5 the patterns of interaction between them and their mother range vastly in diversity, from smooth running and happy to filled with friction and distress of every kind and degree. We also know that these patterns are apt to persist; therefore, the more we know about how they originate the better. It is here that recent research by developmental psychologists has made such huge strides.

PATTERNS OF ATTACHMENT AND THEIR DETERMINANTS

Three principal patterns of attachment present during the early years have now been reliably identified, together with the family conditions that promote them. One of these patterns is consistent with the child's developing healthily, and two are predictive of disturbed development. Which pattern any one individual develops during these years has been found to be profoundly influenced by the way his or her parents (or other parent-type figures) treat him or her. This conclusion, which is as important as it has been controversial, is unpopular in some circles and, in consequence, is constantly challenged. Yet the evidence for it is now weighty and derives from a number of prospective research studies of socioemotional development during the first 5 years. This research tradition was first set by Ainsworth et al. (6–8) and has since been exploited and expanded, notably in the United States by Main et al. (9–11), Sroufe (12,13), and Waters et al. (14,15) and in Germany by Grossmann et al. (16).

The pattern of attachment consistent with healthy development is that of secure attachment, in which individuals are confident that their parent (or parent figure) will be available, responsive, and helpful should they encounter adverse or frightening situations. With this assurance, they feel bold in their explorations of the world and also competent in dealing with it. This pattern is found to be promoted by a parent (in the early years, especially by the mother) being readily available, sensitive to her child's signals, and lovingly responsive when he or she seeks protection and/or comfort and/or assistance.

A second pattern is that of anxious resistant attachment in which the individual is uncertain whether his or her parent will be available or responsive or helpful when called upon. Because of this uncertainty the child is always prone to separation anxiety, tends to be clinging, and is anxious about exploring the world. This pattern is promoted by a parent being available and helpful on some occasions but not on others, by separations, and, later, especially by threats of abandonment used as a means of control.

A third pattern is that of anxious avoidant attachment in which individuals have no confidence that when they seek care they will be responded to helpfully but, on the contrary, expect to be rebuffed. Such individuals attempt to live their life without the love and support of others. This pattern is the result of the individuals' mother constantly rebuffing them when they approach her for comfort or protection. The most extreme cases result from repeated rejection and ill-treatment or prolonged institutionalization. Clinical evidence suggests that, if it persists, this pattern leads to a variety of personality disorders, from compulsively self-sufficient individuals to persistently delinquent ones.

There is much evidence that, at least in families where caregiving arrangements continue to be stable, the pattern of attachment between child and mother, once established, tends to persist. For example, in two different samples (Californian [11] and German [17]) the patterns of attachment to mother at 12 months of age were found, with but few exceptions, still to be present at 6 years. Furthermore, prospective studies in Minneapolis (12) have shown that the pattern of attachment characteristic of the pair when the child was aged 12 months was highly predictive of behavior outside the home in a nursery group 3½ years later. Thus, children who had shown a secure pattern with their mother at 12 months old were likely to be described at 3½ years old by their nursery teachers as cheerful and cooperative, popular with other children, resilient, and resourceful. Those who had shown an anxious avoidant pattern were likely to be described later as emotionally insulated, hostile, or antisocial and as unduly seeking of attention. Those who had shown an anxious resistant pattern were also likely to be described as unduly seeking of attention and as either tense, impulsive, and easily frustrated or passive and helpless.

Ample confirmation of the teachers' descriptions comes from independent observers and laboratory assessments of the same children (12, 18). Similarly, an experimental study done in Germany (19) showed that at 3 years of age children earlier assessed as securely attached responded to potential failure with increased effort, whereas the insecurely attached did the opposite. In other words, securely attached children responded with confidence and hope that they could succeed, whereas the insecure already showed signs of helplessness and defeatism.

In a number of these studies, detailed observations have been made of the way the children's mothers treated them. Great variability was seen, with high correlations between a mother's style of interaction and the child's pattern of attachment to her. For example, in one such study (20), done when the children were 2½ years old, mothers were observed while their children were attempting a task that they could not manage without a little help. Mothers of secure toddlers enabled their children to focus on the task, respected their attempts to complete it on their own, and responded with the required help when called upon. Mothers of insecure infants were less sensitive to the toddlers' state of mind, either not giving support and help when appealed to or else intruding when the children were striving to solve the problem themselves.

In discussing these and similar findings, Bretherton (21) emphasized the easy flow of communication between a mother and her child in secure partnerships and concluded that this easy communication is possible only when a mother is intuitively alive to the crucial part she plays in providing her child with a secure base, variously encouraging autonomy, providing necessary help, or giving comfort according to her child's state of mind.

Mothers of insecure infants deviate from this sensitive pattern of mothering in a great variety of ways. One, common among mothers of avoidant infants, is to scoff at her child's bids for comfort and support (11). Another, well-known to clinicians, the effects of which are now being observed by developmentalists (22, 23), is a mother who fails to respect her child's desire for autonomy and discourages exploration. This is usually a mother who, not having had a secure home base during her own childhood, is consciously or unconsciously seeking to invert the relationship by making her child her own attachment figure. In the past this has too often been labeled "overindulgence" or "spoiling," which has led to appalling confusion about what is best for a child.

It is not difficult to understand why patterns of attachment, once developed, tend to persist. One reason is that the way a parent treats a child, whether for better or for worse, tends to continue unchanged; another is that each pattern tends to be self-perpetuating. Thus, a secure child is a happier and more rewarding child to care for as well as less demanding than an anxious one. An anxious ambivalent child is apt to be whiny and clinging, and an anxious avoidant child keeps his or her distance, is bad-tempered, and is prone to bully other children. In each of these latter cases the child's behavior is likely to elicit an unfavorable response from the parent, so that vicious circles develop.

For the reasons given, patterns, once formed, are likely to persist, but this is by no means necessarily so. Evidence shows that during the first 2 or 3 years the pattern of attachment is a property of the relationship. For example, the pattern of child to mother may differ from the pattern of child to father; also, if the parent treats the child differently the pattern will change accordingly. These changes are among much evidence reviewed by Sroufe (13) that stability of pattern, when it occurs, cannot be attributed to the child's inborn temperament, as has often been claimed. On the contrary, the evidence points unmistakably to the conclusion that a host of personal characteristics traditionally described as temperamental and often ascribed to heredity are environmentally induced. True, neonates differ from each other in many ways. Yet the evidence is crystal clear from repeated studies that infants described as difficult during their early days are enabled by sensitive mothering to become happy, easy toddlers. Contrariwise, placid newborns can be turned into anxious, moody, demanding, or awkward toddlers by insensitive or rejecting mothering. Not only did Ainsworth et al. (6) demonstrate this in their original study, but it has been found again and again in subsequent ones. Those who attribute so much to inborn temperament will have to think again.

Thus, during the earliest years, features of personality crucial to psychiatry remain relatively open to change because they are still responsive to the environment. As a child grows older, however, clinical evidence shows that both the pattern of attachment and the personality features that go with it become increasingly a property of the child himself or herself and also increasingly resistant to change. This means that the child tends to impose it, or some derivative of it, upon new relationships, as with a teacher in the Minneapolis study (12). Similarly, experience shows that the child tends also to impose it or some derivative of it on a foster mother or a therapist.

These tendencies to impose earlier patterns onto new relationships and in some measure to persist in

FIGURE 1. Developmental Pathway Deviating Toward Anxious Attachment and Depression

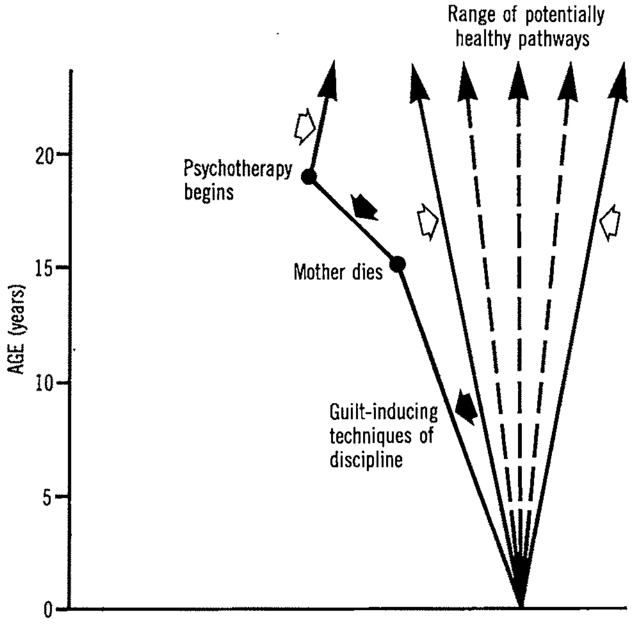
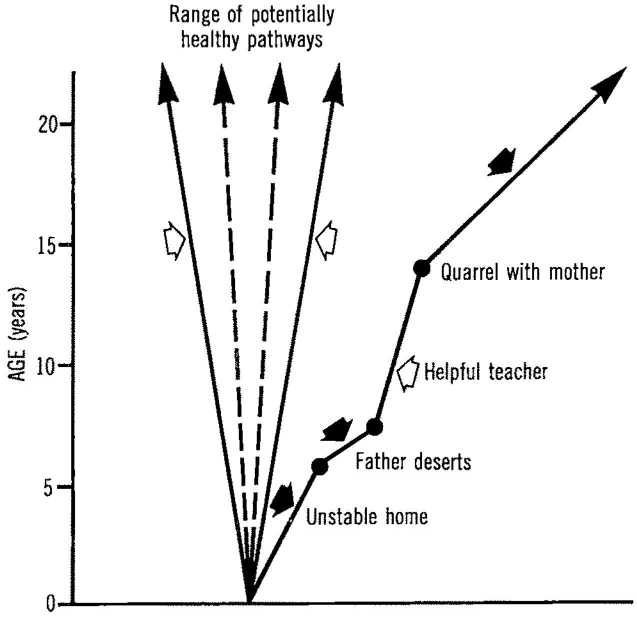

Range of potentially healthy pathways
Psychotherapy begins
Mother dies
Guilt-inducing techniques of discipline
AGE (years)
0
5
10
15
20

FIGURE 2. Developmental Pathway Deviating Toward Hostility and Delinquency



doing so despite absence of fit are, of course, the phenomena that gave birth to psychoanalysis. They are also the phenomena that during recent decades have led an increasing number of analysts to embrace an interpersonal or object relations version of psychoanalytic theory and, in my own case, to advance the attachment version with its postulate of internal working models of self and attachment figure in interaction. Thus far, therefore, the picture presented can be looked upon as a much modified and updated variant of traditional psychoanalytic thinking in which great emphasis is placed on the particular pattern into which each personality comes to be organized during the early years, with its own distinctive working models (or, to use the traditional term, "internal world") and on the strong influence thereafter that each individual's models have in shaping his or her life.

CONTINUITY AND DISCONTINUITY: VULNERABILITY AND RESILIENCE

One of the long-running debates between analysts and others in our field turns on the extent to which it is believed that personality, once developed during the early years, is open to change. Analysts have emphasized a strong tendency toward stability and continuity and have explained it as due to the powerful influence of the individual's existing internal world on how he or she construes and responds to every new situation. Critics have emphasized the extent to which an individual's performance can change given changed conditions of life. If we are to do justice to the plethora of data now available, we must abandon simple dichotomies. First, a sharp distinction must be drawn between current functioning, measured in terms of presence or absence of psychiatric disorder, and personality structure, measured in terms of greater or less vulnerability to adverse life events and situations. Linked closely to degrees of vulnerability, moreover, are the very different ways that people feel about their lives, either as mostly enjoyable and to be lived to the full or else as a burden to be endured, as an emotionally rich and varied experience or an emotional desert.

Second, we have at all times to think in terms of the interactions and transactions that are constantly occurring between an ever-developing personality and the environment, especially the people in it. This means that it is necessary to think of each personality as moving through life along some developmental pathway, with the particular pathway followed always being determined by the interaction of the personality as it has so far developed and the environment in which it then finds itself. If as developmental psychiatrists we adopt these ways of thinking, we need to picture each personality as moving through life along its own unique pathway. So long as family conditions are favorable, the pathway will start and continue within the bounds of healthy and resilient development, but should conditions become sufficiently unfavorable at any time, it may deviate to a lesser or greater extent toward some form of disturbed and vulnerable development. Conversely, should an infant be born into unfavorable conditions, the pathway along which it develops may become deviant very early; yet once again, should there be change, in this case for the better, there is a chance of the deviation diminishing to a lesser or a greater extent. Examples of two such deviant pathways are illustrated in figures 1 and 2.

This leads me back to patterns of attachment, since my hypothesis is that the pathway followed by each developing individual and the extent to which he or she becomes resilient to stressful life events is determined to a very significant degree by the pattern of attachment he or she develops during the early years. Furthermore, this implies that, in identifying the family experiences that result in different children developing different patterns of attachment, my colleagues are identifying also some of the major determinants of each person's future resilience or vulnerability to life's hazards as well as the extent to which he or she will be able to enjoy life.

To date, unfortunately, the detailed prospective studies described earlier of how some of the different patterns of attachment come into being and of their relative persistence have so far not been carried beyond the 6th year. This means that the hypothesis, however plausible, will be without rigorous testing for some years yet. Meanwhile, however, backers of the hypothesis point to much supporting evidence coming from the other major school of research referred to earlier in this paper—namely, epidemiological studies of adults who are suffering from one or another of a wide range of psychiatric disabilities, including anxiety and depressive states, suicidal behavior, borderline conditions, and sociopathic personality.

From among a large array of epidemiological studies I have chosen the work of George Brown and Tirril Harris to illustrate my thesis because it not only is of the highest quality but also pays attention to variables of the kind that the prospective research already described is showing to be so very influential. In addition, they are using a sophisticated model of developmental pathways for interpreting their findings.

Brown and Harris have studied no fewer than four large representative samples of the female population, two in inner London boroughs, one in an outer borough, and one in a remote rural area of the Scottish Highlands. (In two of their studies they explored the effects of loss of the father during childhood because there is often a higher incidence of such loss among samples of depressed women than among control subjects. Since detailed analyses show that loss of the father has much less influence on vulnerability than loss of the mother, further reference to it is omitted.) The aim of these researchers has been to identify women suffering from depression of a clinically significant degree and to compare them with other women in the same community who are not depressed in order to discover whether there are any family or other social variables that distinguish the two groups. The findings of the first such study, done in the inner London borough of Camberwell, were published 10 years ago (24) and are becoming well-known. In it they identified four classes of variables that were found significantly more often among the depressed members of the population. Three of these concerned *current* events and conditions: 1) a severe adverse event, usually involving an important personal loss or disappointment, that had occurred within the year before onset, 2) the absence of a companion in whom to confide, and 3) chronically difficult living conditions, including extremely bad housing and responsibility for caring for a number of children under the age of 14.

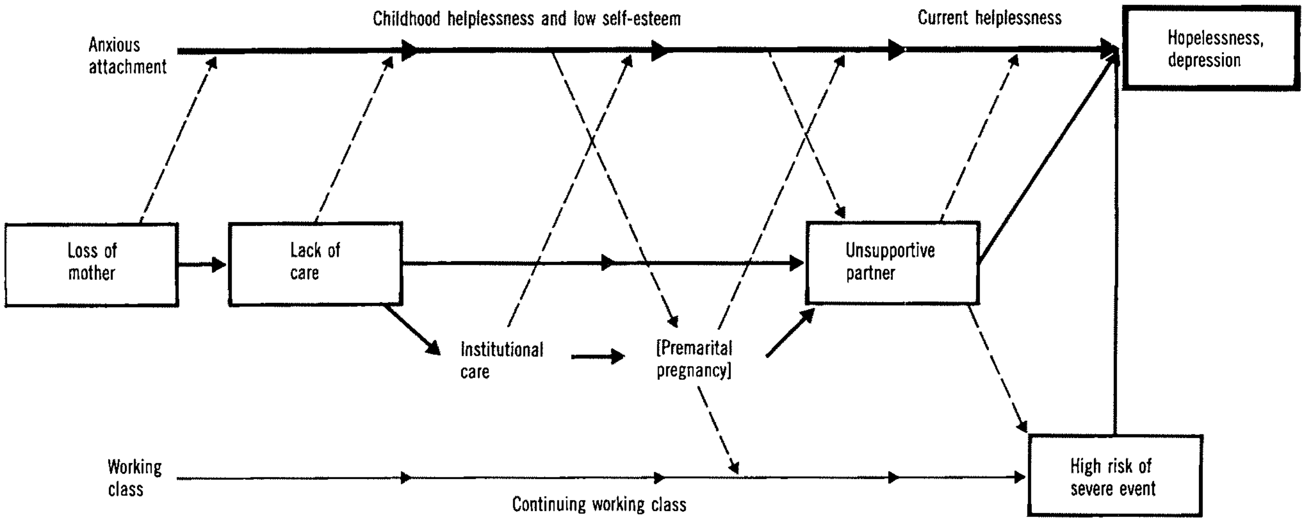
The fourth variable associated with current incapacitating depression is a *historical* one—namely, a woman's loss of her mother due to death or prolonged separation before her 11th birthday. In subsequent studies of two other large and mainly working-class samples, in Walthamstow and Islington (25–28), findings of a similar sort have been the rule. The incidence of a current affective disorder in women who had lost their mother before their 11th birthday compared with those who had not done so were, in the three samples, 43% versus 14%, 25% versus 7%, and 34% versus 17%, respectively. Moreover, in the second and third studies (26, 27) it was found that women who had lost their mother during adolescence (between their 11th and 17th birthdays) were also more prone to develop depression than control subjects, although less so than those who had lost their mother when they were younger. The consistency of these findings, together with findings from a long-term prospective study reported by Wadsworth (29), gives strong support to the clinically derived hypothesis that childhood loss of one's mother is likely to lead a person to become excessively prone to develop psychiatric symptoms and to do so especially when current personal relationships go wrong.

In their Walthamstow study (27), members of the Brown-Harris group undertook a prolonged and extensive interview with each woman in order to gain as much information as possible about the family circumstances during her childhood and adolescence and also about her subsequent life course, including, for example, the jobs she had had, her boyfriends, any premarital pregnancy, and her husband and children (if any). With the sample deliberately structured to include a high proportion of women who had suffered a childhood loss or prolonged separation, it became possible to analyze the extent to which family variables other than loss may have contributed to a woman's current vulnerability.

In keeping with expectations it was found that both the family circumstances which had led to the childhood loss and the adequacy of care the girl had received afterwards were of great consequence. The worse the family circumstances before the loss and the more inadequate the care after it the more vulnerable to depression the woman had become.

The very detailed analyses of these data carried out by the researchers have led them to explain their findings in terms of developmental pathways that, through the continuing interactions of social and personality factors, result in a working-class woman in London who loses her mother for any reason to be at an appallingly high risk of becoming depressed. In the first place, they found, such a loss carried with it a high likelihood that she will not receive adequate care; in

FIGURE 3. Female Pathways to Depression[a]



[a] Adapted from Harris et al. (27)

the Walthamstow study (27) the chances were found to be no better than 50–50. Subsequently, her troubles were likely to snowball. Should the care she received have been poor, risks were high that she would become pregnant before marriage and/or that she would venture on an early and ill-advised marriage. These two occurrences were found to be strongly associated with later depression, in part because they usually resulted in her living in very unfavorable conditions at high risk of suffering a severe adverse event and with no one in whom to confide. For these reasons a working-class woman who had lost her mother was all too likely to find herself on a slippery slope.

Figure 3, adapted from one designed by Harris et al. (27), attempts to illustrate these interacting processes. The thick upper line represents the woman's mental state. The middle line represents what may for convenience be described as her family environment. The thin lower line represents her socioeconomic environment, in this case urban working class. The broken lines indicate the endless ways in which mental state and environment interact, with environmental happenings affecting mental state and mental state, in turn, affecting the way the girl or young woman deals with aspects of her environment.

Two further findings, both from the Islington study (28), illustrate this interaction. A woman who had received inadequate care, either in or out of her family, was found to be twice as likely to have developed a negative self-image as a woman who had received adequate care. The figures were 54% compared with 27%. Similar differences have been reported from Edinburgh (30).

Furthermore, the marriage she had entered into was more likely to have failed than was that of the more fortunate woman. Here the figures were 36% and 23%. The high risk of this happening was evidently the result of a chain of adverse happenings. For example, when a young woman has no caring home base she may become desperate to find a boyfriend who will care for her. That, combined with her negative self-image, makes her all too likely to settle precipitately for some totally unsuitable young man. Premature pregnancy and childbirth are then likely to follow, with all the economic and emotional difficulties entailed. Moreover, in times of trouble, the effects of her previous adverse experiences are apt to lead her to make unduly intense demands on her husband and, should he fail to meet them, to treat him badly. No wonder one in three of these marriages broke up.

Gloomy though these conclusions are, we must remember always that a disastrous outcome is not inevitable. The more secure an attachment a woman has experienced during her early years, we can confidently predict, the greater will be her chances of escaping the slippery slope.

CONCLUSIONS

In conclusion, I refer, first, to some of the many scientific problems that clamor for attention and, second, to some of the practical implications of our present knowledge.

A first scientific task is to explore and test the hypothesis, stated earlier, that each person's resilience or vulnerability to stressful life events is determined to a very significant degree by the pattern of attachment he or she develops during the early years and, more especially, to clarify to what degrees and in what ways the early-developed patterns influence subsequent development. Since, however, there are many subpatterns of each of the three main patterns, to elucidate the influence of each will be a long and time-consuming task. An integral part of such research is the further examination of precisely what environmental conditions, impinging earlier and/or later, enable a person to retain or attain a greater degree of resilience and, conversely, what conditions push him or her toward greater degrees of vulnerability.

Yet another substantial group of variables to be taken into account are the heritable differences that must be assumed to exist between different individuals in their capacity to deal with the various environmental hazards, especially inadequate parenting, which influence vulnerability.

In undertaking such a series of research programs, an early requirement is the development of psychological methods for assessing patterns of attachment and their derivatives at each phase of the life cycle. Main et al. (11) and other developmental psychologists are already making some promising moves in this direction. To cast light on problems of continuity and discontinuity, both of patterns of attachment and also of different degrees of resilience and vulnerability, prospective studies following personality development through different phases of the life cycle and in different environments are plainly indispensable, despite their being very costly.

This brief sketch represents what will be an enormous program of research in developmental psychopathology (31), one that will clearly require generations of research workers. Both in magnitude and in the biological principles informing it, it can best be compared to the vast program of research that has been and is still being undertaken in immunology. Here, as in our own field, research workers are concerned with the extraordinarily complex interactions and transactions that occur between an organism as it develops over the years and the array of hazards present and potentially present in its environment. Concepts analogous to those in our field include the degree to which an organism is immune to a wide variety of hazards and the extent to which an existing state of immunity will persist or change over time.

What then are the practical implications of our present knowledge? For the clinician concerned with the assessment and treatment of a wide range of psychiatric patients of all ages it provides a developmental psychopathology that is biologically based, coherent, and already empirically well supported. As such it can provide guidance for understanding how a patient's problems and symptoms have evolved in his or her transactions with the particular environments he or she has encountered from infancy to the present day, thus providing an updated and detailed version of the life chart, which Adolf Meyer (32) so rightly advocated. Furthermore, it can provide guidance also for planning therapeutic intervention. Although much detailed work is still required in these areas, promising starts have been made (33–36).

What, however, is even more important (and would be especially welcome to Adolf Meyer) is the firm guidance it gives for prevention. As I have emphasized throughout, I believe there is already sufficient evidence, coming from diverse and independent sources, that points to the very substantial influence on personality development and mental health of the way an individual's parents (or in some cases parent substitutes) treat him or her. Given affectionate and responsive parents who throughout infancy, childhood, and adolescence provide a boy or girl with a secure base from which to explore the world and to which to return when in difficulty, it is more than likely that a child will grow up to be a cheerful, socially cooperative, and effective citizen and to be unlikely to break down in adversity. Furthermore, such persons are far more likely than those who come from less stable and supportive homes to make stable marriages and to provide their children with the same favorable conditions for healthy development that they enjoyed themselves (37, 38). These, of course, are age-old truths, but they are now underpinned by far more solid evidence than ever before.

Unfortunately, as we also know, there is another and less happy side to the picture. Children and adolescents who grow up without their home base providing the necessary support and encouragement are likely to be less cheerful, to find life—especially intimate relationships—difficult, and to be vulnerable in conditions of adversity. In addition, they are likely to have difficulties when they come to marry and have children of their own. It is fortunate, of course, that despite these handicaps some manage to struggle through, though often at a much greater cost to their emotional life than meets the undiscerning eye. Nor must the fortunate exceptions blind us to the rule. Thus, to take an analogy from physiological medicine, the fact that some heavy smokers survive is no argument for continuing to use tobacco.

In this paper I have described how I see the state of developmental psychiatry today. On this basis I think we can claim it has now come of age.

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Significance and Meaning of Neurological Signs in Schizophrenia

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The authors review studies of abnormal signs on clinical neurological examination of schizophrenic patients. In spite of a number of methodologic limitations, the cumulative evidence strongly argues that there are more neurological signs in schizophrenic patients than in nonpsychiatric control subjects. Although less consistent, there is considerable evidence of more neurological signs in schizophrenic patients than in patients with affective disorders or with mixed, nonpsychotic disorders. The existing literature suggests several preliminary hypotheses with respect to neuroanatomical localization of neurological signs, subtyping of schizophrenia, and utility of studies of relatives at high risk and family history studies. Directions for future research in these areas are described.

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Theories of the etiologies and pathogenesis of schizophrenia have long posited a significant role for brain dysfunction. In recent years increasingly sophisticated neuroanatomical, neuroradiological, neurophysiological, and neuropsychological studies have been pursued. However, the nature of neurological impairment that can be elicited and characterized by the clinical neurological examination remains uncertain. Although there is a long history of anecdotal reports and clinical descriptions (1, 2), it is only in the last 25 years that a number of systematic surveys and controlled studies of neurological impairment in schizophrenia have been reported. However, the interpretation of this work is complicated by variable methodology and conceptual confusion. The latter is illustrated by the use of the term "soft signs" in describing many of the abnormal neurological findings in these studies. This designation encourages disinterest by implying that the abnormalities reported are ambiguous, unreal, fleeting, nonreproducible, nonlocalizing, and uninterpretable. Yet for the most part the abnormalities in question are elicted by standard items of the clinical examination. That their meaning in schizophrenia is uncertain reflects not the unreality of findings but limitations in our knowledge.

In this article, studies of neurological abnormalities based on clinical examination of adolescent and adult schizophrenic patients will be reviewed. After considering the prevalence of neurological signs in schizophrenia—especially compared to the prevalence in normal subjects and patients with other psychiatric disorders—we will consider the significance of these signs with respect to neuroanatomical localization, clinical subtyping, and studies of family history and relatives at high risk.

RELATIVE PREVALENCE OF NEUROLOGICAL SIGNS IN SCHIZOPHRENIA

The relative prevalence of neurological signs in schizophrenic patients has been the basic issue that most studies have sought to address. These studies have used various assessment procedures but can be divided into two broad categories: those using a comprehensive neurological examination that assesses a wide range of neurological competency and those using a selective examination that focuses on a smaller number of neurological items or specific dimensions of interest. Six studies (3–9) used comprehensive examinations to compare schizophrenic patients either to patients with other psychiatric diagnoses or to nonpsychiatric control subjects. The majority of these studies demonstrated a higher prevalence of neurological abnormalities in schizophrenic patients than in patients with mixed psychiatric disorders, i.e., personality, neurotic, and substance abuse disorders (3–6, 9), and affective disorders (6, 9); in monozygotic twins discordant for schizophrenia (7); and in nonpsychiatric control subjects (3–5, 9). In the studies that reported a specific prevalence, the rate of neurological abnormality was between 50% and 65% in schizophrenic patients (4–6) but was only 5% in nonpsychiatric control subjects (4–6). The difference between schizophrenic patients and mixed diagnostic groups failed to reach statistical significance in one of the studies (6) and was significant for females, with only a trend for males, in another (4, 5). In the latter study the weak-

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ening of the difference for males was thought by the authors to reflect differences in diagnostic practices for male and female patients. Furthermore, in the study by Woods et al. (9), the difference between schizophrenic patients and substance abusers disappeared when a more restricted definition of neurological dysfunction was used. Kolakowska et al. (8) were unable to find any difference between schizophrenic and schizoaffective patients, and Kennard (3) was unable to differentiate schizophrenic adolescents from those with organic impairment on the basis of neurological examination.

Thirteen studies (10–23) used a selective examination to determine the relative prevalence of neurological signs in schizophrenia. Again, as with the comprehensive studies, the majority of these studies demonstrated a higher prevalence of neurological abnormalities in schizophrenic patients than in patients with mixed psychiatric disorders (10–12, 14) and affective disorders (11, 12, 15–19, 23) and in nonpsychiatric control subjects (11–14, 16–19, 23). Only two studies reported specific prevalence rates: 58% of schizophrenic patients had mild to moderate neurological impairment compared to 32% of an unspecified nonschizophrenic group of psychiatric patients in a study by Tucker et al. (10), and Manschreck and Ames (23) reported neurological signs in 92% of schizophrenic patients, but in only 52% of patients with affective disorders and in just 5% of control subjects. However, there are conflicting results. Cox and Ludwig (11), using an assessment organized according to the cerebral lobe, in which the domain of functioning tapped by the neurological sign is presumed to be dependent, were only able to detect a difference between schizophrenic and unipolar depressive patients on frontal lobe-dependent signs. Weller and Kugler (13) found no difference between acute and chronic schizophrenic and schizoaffective patients, and on only one measure did acute, but not chronic, schizophrenic patients differ from affective disorder patients. Finally, Nasrallah et al. (22) found no significant differences between schizophrenic and bipolar patients, although there was more impairment in the former.

In sum, the results of these studies demonstrate, without exception, a higher prevalence of neurological signs in schizophrenic patients than in nonpsychiatric control subjects. These results persist regardless of the type of assessment procedure used. Furthermore, the preponderance of data suggests that schizophrenic patients have more neurological abnormalities than patients with mixed psychiatric disorders and affective disorders.

METHODOLOGICAL ISSUES AND CONFOUNDING VARIABLES

The consistency across studies of the finding of more neurological signs in schizophrenia is compelling. However, these studies were conducted over a 25-year period in which standards for research methods in psychiatry have changed dramatically. Hence a consideration of a number of important methodological issues is warranted.

Sample Size

The number of schizophrenic patients participating in the studies of neurological signs considered in this review ranged from 16 to 114, influencing the confidence with which positive and, especially, negative findings can be accepted. Of these studies, two had fewer than 20 schizophrenic subjects (15, 17), 11 studies had between 20 and 39 (6, 7, 9, 11, 12, 14, 16, 18, 19, 24–27), five had between 40 and 59 (8, 13, 20–23), and five had over 60 schizophrenic subjects (4, 5, 10, 28–31).

Diagnosis

The studies under review used various diagnostic criteria, including "Bleulerian primary criteria" (7), *DSM-II,* Schneiderian first-rank symptoms (10, 13, 24, 27, 32), the New Haven Index (10, 24, 27, 33), the criteria of Brown et al. (34), the Research Diagnostic Criteria (RDC) or Feighner criteria (8, 11, 15–17, 19, 25, 30, 31, 35, 36), and *DSM-III* (9, 18, 20–23). Five studies (3–6, 26, 29) provided no specified criteria. In sum, only 13 of 23 studies used acceptable modern diagnostic criteria. The use of older diagnostic criteria or unspecified criteria in many of the earlier studies (3–7, 10, 13, 14, 24, 26–30) raises a concern about their comparability with those using modern diagnostic criteria (8, 9, 11, 15–23, 25, 30, 31). However, the conclusions reached by both groups of studies are similar with respect to relative prevalence and, as discussed later, areas of dysfunction and relationship to cognitive impairment. When discrepancies have occurred between studies, diagnostic criteria do not appear to be the source of discrepancy.

Reliability

Over the time in which these studies were done there has been a growing appreciation of the importance of reporting the reliability of assessment measures. However, only 10 of the 23 studies (7, 9, 11, 12, 15, 17–19, 23, 25, 29) provide information about either simultaneous or test-retest reliability, and the majority provide no details about the procedure for reliability assessment. Correlation coefficients ranged from 0.60 to 0.98 for total scores. Since any individual neurological sign is a relatively rare event, typically scored as either present or absent, designing adequate assessments of item reliability has been difficult.

While the reliabilities reported are generally in the highly acceptable range, only the Quitkin et al. (29) study describes a detailed and rigorous reliability exercise. Clearly, there is the need for further well-described assessments in this area. However, when viewed together with the more rigorous examinations of reliability in the child psychiatry literature (37), there is the strong likelihood that the type of neurological signs reported in the schizophrenic population can be rated reliably.

Temporal Stability

Little attention has been paid to the stability or progression of neurological impairment in schizophrenic patients over time or to the extent to which they are a state phenomenon tied to fluctuations in the clinical status of patients. Tucker and Silberfarb (27) reported on the retesting of their patients 3 years after the initial neurological assessment. Although they found the neurological index to decrease for both schizophrenic and nonschizophrenic subjects, the decrease was significant only for the nonschizophrenic subjects. Unfortunately, only group comparisons were provided, and the stability of neurological signs within individual subjects was not evaluated. Torrey (30) reported that in his subchronic/chronic group, retested after 2–10 months, four of six patients equivocal for the presence of neurological signs had demonstrable signs, and 20 of 24 patients positive for the presence of neurological signs remained so. In the acute group, three of four patients who had had equivocal signs had no signs of neurological impairment at retesting. Unfortunately, test-retest results on other cases are not available. Furthermore, neither of these studies assessed the reliability of their assessment measures. In addition, Torrey (30), in an apparent contradiction to the above data, which support the concept of neurological impairment as a trait characteristic, gave his impression, without data, of a positive correlation between neurological signs and clinical state. Manschreck et al. (18) found no difference in neurological signs between inpatients and outpatients, groups that would presumably differ in clinical state. It is noteworthy that moderate stability of neurological signs from childhood to adolescence has been demonstrated in the offspring of schizophrenic patients (38). Although the available data favor the idea of neurological impairment as a stable trait characteristic, the studies are flawed, the possibility of progression is not examined, and the potential of the clinical state affecting the assessment of stability is not adequately evaluated.

Medication

It is necessary to determine the extent to which neuroleptic medications alter the manifestation of neurological signs. Eight studies (11–13, 15–17, 19, 23, 25) have compared schizophrenic patients taking neuroleptics to those drug free at the time of assessment and have shown no difference in the prevalence of neurological signs between groups. In addition, Mosher et al. (7) reported no relationship between neurological signs and either current or lifetime neuroleptic use; Kolakowska et al. (8) found no relationship between neurological signs and dose of neuroleptic, extrapyramidal side effects, or tardive dyskinesia, and Wegner et al. (31) noted that length of exposure to neuroleptics had no effect on the number of neurological signs present. Manschreck et al. (18) actually reported fewer motor abnormalities in medicated as contrasted to drug-free patients. Quitkin et al. (29) divided their schizophrenic subjects into those with premorbid asociality and other mixed syndromes. There was no difference in neurological signs between patients with premorbid asociality who were or were not taking neuroleptics, whereas medicated patients with other mixed syndromes had more signs than those who were drug free. The authors explained the greater number of neurological signs in medicated patients with other mixed syndromes as being either a medication effect or that patients with other mixed syndromes who required medication at the time of assessment (the authors attempted to discontinue medication in all patients) represented a subgroup more prone to neurological abnormalities. Mukherjee et al. (39), in a study of bipolar patients, argued that neuroleptics may induce neurological signs; however, the clinical similarity to schizophrenia of patients receiving neuroleptics may better explain the apparent correlation between neuroleptic exposure and the presence of neurological signs.

Extrapyramidal motor abnormalities have played only a minor role in neurological assessments, given the presumption that they are most often drug effects. A study by Owens and Johnstone (40), however, challenges this view. They found such abnormalities in 327 of 456 chronic schizophrenic patients, including 27 of 52 patients with no history of neuroleptic use. Furthermore, in the total sample these motor abnormalities were significantly correlated with negative symptoms, cognitive impairment, and poor behavioral performance. However, this was an older sample (the mean age for patients without a drug history was 70 years) in which age-related neurological changes would be expected to play an important role.

The evidence currently available predominantly argues that medication does not alter neurological signs, although it may be an important confounding variable in some subgroups (29). However, these are all between-subject comparisons in which medication status is not an experimentally controlled variable. Differing clinical factors presumably determine which patients are medicated at the time of assessment. In most cases these factors are unspecified, although clearly these patients differ in important ways. A definitive study of the effect of neuroleptic medication would ideally involve an assessment of the same patients both while they are receiving medication and after medication is discontinued. An alternative would be to compare similar patients randomly assigned to medicated and nonmedicated status. To our knowledge, neither strategy has appeared in the literature to date.

Demographic Variables

Age, sex, socioeconomic status, and race are potentially significant confounding variables that have received little attention. Three studies (7, 8, 13) have shown no correlation between age and neurological impairment. On the other hand, Tucker et al. (10) reported a positive correlation with age across the total patient sample (schizophrenic and nonschizophrenic). Torrey (30) found a nonsignificant trend toward a positive relationship, and Manschreck and Ames (23) demonstrated sensory disturbance to be positively correlated with age. However, most studies fail to give the age range of their patient populations, and it may be the case that the range is too narrow to adequately evaluate or detect an age effect. Thus, no firm conclusions can be reached about the effect of age on neurological signs. Similarly, the influence of sex on the prevalence of neurological signs has not been well studied. Three studies (4, 5, 8, 24) found no sex-related differences, although Hertzig and Birch (4, 5) noted slightly more impairment in males. Rochford et al. (6) reported significantly more, and Manschreck and Ames (23) reported a trend toward more neurological impairment in men. If a sex difference does exist, it would appear to be in the direction of more neurological signs in men; however, only two studies (8, 23) used a comprehensive examination and modern research criteria, and their results are in conflict. Two studies have examined the effect of socioeconomic status. Rochford et al. (6) found no relationship, but Manschreck and Ames (23) reported fewer neurological signs in educated patients. They suggest that this may be explained by a greater proportion of paranoid patients in the more educated group. To our knowledge, no studies have looked at the effect of race, nor have cross-cultural comparisons been undertaken. Clearly, more study is required to elucidate the need to control for these demographic features.

NEUROANATOMICAL LOCALIZATION AND BRAIN MECHANISMS OF DISEASE

While a considerable number of neurological signs have been reported in schizophrenic patients, there is the frequent assumption—reflected in the characterization of many of these abnormalities by the term "soft signs"—that they are present in an unsystematic and intrinsically nonlocalizable manner. However, studies that have used a comprehensive assessment of neurological signs have shown some types of signs to be quite frequent, but not others. Furthermore, studies that have used a more focused assessment based on prior comprehensive evaluations have supported the notion of there being more discrete areas of functional impairment.

The majority of the comprehensive studies have found more abnormalities in the area of integrative sensory function. This is reflected in the higher rates of bilateral extinction (4, 5, 29); impaired audiovisual integration, assessed by matching auditory with visual patterns (4, 5); agraphesthesia (6, 29); and astereognosis (6). This is further supported by nine more focused studies (10–15, 19, 20, 21, 23–25) that examined dysfunction in this area. In contrast, tests of more primary sensory capacities showed few abnormalities.

Most of the comprehensive studies have also found more difficulties in the area of motor coordination, including intention tremor (3, 9), balance and gait (4, 6, 9), hopping (29), finger-thumb opposition (29), dysdiadochokinesis (11), and general coordination (4–6). In addition, three focused studies (15, 19, 25) confirmed more abnormalities in this area. This contrasts with a failure to find more abnormalities in motor strength or, with two exceptions (3, 9), in deep tendon reflexes.

The sequencing of complex motor acts has not been well examined in the comprehensive studies. However, a series of reports by Manschreck et al. (16–18, 23) note more abnormalities of this sort in schizophrenic patients. Their assessment procedure included the fist-edge-palm test, fist-ring test, and the Ozeretski test, adopted from Luria (41), all of which assess the subject's ability to perform repetitive alternations in hand positions. For example, in the fist-edge-palm test the subject is required to alternate touching the table with his or her hand in the shape of a fist, extended with the side of the hand down, and extended with the palm of the hand down. Schizophrenic patients are more prone to demonstrate significant disruptions in patterning these movements, such as perseverating in one position. Since the sequencing of motor acts is thought to depend on systems that heavily involve the frontal lobes, additional support for difficulty in this area comes from two studies (11, 12, 20, 21) that used similar items designed to test frontal lobe functioning.

It would be important to know whether abnormalities in each of these functional systems—sensory integration, coordination, and motor sequencing—occur together in a subgroup of neurologically impaired schizophrenic patients or whether several subgroups are characterized by impairments in different systems. Unfortunately, there is little basis in the existing literature for choosing between these alternatives. There has been only a slim effort to characterize patterns of signs in individual patients, and in most studies the statistical power to demonstrate such relationships was quite limited. Four studies (4, 5, 9, 11, 25) sought, but did not find, a pattern of signs or correlation between individual signs, whereas Manschreck and Ames (23) found that the presence of motor abnormalities positively correlated with sensory integrative impairments.

There have been attempts to use electrophysiological and brain imaging techniques to more accurately localize the defects responsible for abnormal neurological signs in schizophrenia. However, they have been largely unsuccessful. Four studies sought to determine a relationship between neurological signs and EEG abnormalities. In three cases no relationship was found (3, 7, 30), and in the fourth the only relationship was with nonspecific phenothiazine-induced paroxysmal EEG abnormalities (28). Three studies examined the relationship between neurological signs and CAT scans. Two studies (8, 30) found no relationship. Weinberger and Wyatt (26) did find a relationship between neurological signs and enlarged ventricles on CAT scan, although ventricle enlargement has little localizing significance.

In sum, the most basic mechanisms of sensory input and motor output do not appear to be disturbed. Impairments are found in three higher-order functional areas: the integration of more complex sensory units, the coordination of motor activity, and the sequencing of motor patterns. While one might be tempted to postulate that these areas reflect abnormalities in the parietal lobe, the cerebellum, and the frontal lobe, respectively, this would be an unwarranted and undoubtedly erroneous simplification. It is more accurate to posit that there are impairments in several functional systems that include in their neurological substrate the previously mentioned regions. The actual location of the neurological defect need not be at these sites but may involve components of these systems at other levels of the neuroaxis. Indeed, several of the authors suggest that the problem is likely to be subcortical, either in the basal ganglia and brainstem (3) or in the limbic system (7). Indirect support for subcortical localization is provided by the failure of EEG and CAT scan studies to find evidence of cortical abnormalities in association with neurological signs, and subcortical localization is compatible with the theories of workers such as Stevens (42). Seeking to understand neurological abnormalities in terms of anatomically distributed but discrete functional systems is in keeping with current speculations about neurological organization (43–46).

NEUROLOGICAL SIGNS AND THE HETEROGENEITY OF SCHIZOPHRENIA

The heterogeneity of schizophrenia has led to the development of more specific diagnostic criteria and the search for more homogeneous subgroups within the schizophrenic syndrome. Various biological markers have been studied to assess their utility in defining meaningful subgroups. A potential role for the presence or absence of neurological abnormalities as such a marker of specific symptom profiles or courses of illness has received some attention.

The strongest case for a relationship between neurological signs and a symptom dimension is in the area of thought disorder and cognitive impairment. Neurological abnormalities in schizophrenic patients have been shown to be correlated with bizarreness and distractibility (6), formal thought disorder (16–18, 23), overinclusive thinking (10), lower IQ (3, 7, 23), impairment on the Bender-Gestalt battery (3), decreased type-token ratio (16), and impaired performance on the Mini-Mental State Exam (23). In addition, Tucker et al. (10, 24) found the presence of thought disorder to be related to neurological signs across a mixed group of psychiatric patients regardless of diagnosis. The consistency of this association of neurological signs with measures of thought disorder and other cognitive variables, combined with an absence of negative findings, argues strongly that neurological signs identify a subgroup of schizophrenic patients with more cognitive impairment.

However, it is possible that the relationship between neurological signs and cognitive impairment is not specific, but rather reflects an association between neurological abnormality and more severe pathology in general. The evidence in this regard is mixed. Neurological signs were not related to overall presence of positive symptoms (8), number of rehospitalizations during a 3-year follow-up (27), overall clinical outcome (8), total lifetime hospitalization (7), history of neuroleptic or ECT use (7), neuroleptic response (8), or inpatient versus outpatient status (18). On the other hand, neurological abnormalities have been related to behavioral ratings at the time of assessment (7), number of psychiatric symptoms (27), longer index hospitalization (6), and number of previous hospitalizations (10).

The relationship between neurological signs and other symptom profiles is less clear. There is some evidence to suggest that neurological signs are more prominent in patients with negative symptoms. Neurological abnormalities have been shown to be correlated with withdrawal (6) and blunted affect (18). However, one study (8) failed to find a relationship between neurological signs and the presence of either negative or positive symptoms. The association between neurological signs and the paranoid/nonparanoid distinction is disputed, with less neurological impairment in paranoid patients in one study (18) and no difference in another (23).

Neurological abnormalities have been found to be more characteristic of a chronic rather than an acute course of illness (13, 30). Chronic, as opposed to acute, schizophrenia has often been characterized as a progressively deteriorating condition, and it is possible that neurological signs increase over time as a concomitant of this process. In support of this notion, two studies reported a relationship between neurological signs and duration of illness (8, 30). However, in one of these (8), the association disappeared when more stringent criteria of abnormality were employed. In addition, two studies found no such association (9, 13). Until the stability of neurological abnormalities and their correlation with age is established, the question of their progression will remain unanswered.

Other relationships with features of the course of illness have not been consistently demonstrated. An association between neurological signs and an early age at onset was shown in two studies (9, 30) but not in two others (3, 8); however, in one of these studies

(3) an exclusively adolescent sample was used, and all of the subjects could be considered as having an early onset. Patients with impaired premorbid functioning were noted to have more neurological signs in one study (29), but this was not replicated in three others (8, 10, 30).

In sum, neurological abnormalities have been shown to be most clearly associated with thought disorder and cognitive impairments, as well as with the chronic form of the illness. The relative lack of association with the duration of illness and the results of studies of family history and studies of relatives at high risk, to be discussed next, suggest that neurological abnormalities may predate the identifiable onset of the schizophrenic illness and predict a chronic, debilitating course.

STUDIES OF FAMILIES AND HIGH-RISK GROUPS

Little effort has been made to use neurological signs to characterize subgroups of patients that might be homogeneous with respect to factors of alleged etiological significance in schizophrenia. Such effort has focused exclusively on genetic factors. Two basic approaches have been taken. The first approach examines the relationship between neurological signs and family history. In the only study designed specifically for this purpose, Walker and Shaye (25) found more neurological signs in schizophrenic patients with a family history of schizophrenia than in those without such a history. While two other studies failed to find this relationship (8, 30), neither was designed to test this question, and the power of the post hoc analyses to find such a relationship is uncertain. The other approach is to study family members for the presence of neurological abnormalities. The study of relatives at high risk is an example of this kind of analysis. Fish (47–52 and an unpublished paper, 1980) described her experience of serial neurological assessments beginning in infancy of the offspring of schizophrenic and nonpsychotic mothers. While she did not find a stable neurological defect, she reported a pattern of erratic neurointegrative development over time. This maturational dysfunction, termed a "pan-developmental" retardation, was significantly more frequent in the offspring of schizophrenic mothers and was associated with serious psychopathology, including psychosis, later in life. Marcus et al., in an Israeli high-risk study (53, 54), reported that children who were younger than 11 years of age and had a schizophrenic parent had more neurological abnormalities than matched control subjects. This difference reached significance in a "median split analysis" that compared the more deviant half of each group. This analysis was employed because only a portion of the offspring would be expected to have the vulnerability to the illness. Impairments were prominent in fine motor performance, right-left orientation, motor coordination and overflow, and sensory integration. Marcus et al. found a similar excess of neurological dysfunction in the offspring of a Danish sample (38). They (55) also reported on a subgroup of infants born of schizophrenic mothers and found them to be characterized by poor motor and sensory performance throughout the first year of life. Rieder and Nichols (56) considered the neurological and psychological status of 7-year-old children. More neurological abnormalities were found in male children with a schizophrenic parent than in control male children on the basis, primarily, of increased problems in coordinating hand and arm movements. In addition to the findings in the offspring of schizophrenic patients discussed earlier, Kinney et al. (57) demonstrated more neurological abnormalities in the relatives, primarily siblings, of schizophrenic patients. Furthermore, a retrospective study of child guidance clinic records (58) found more reports of neurological abnormalities in children who later developed schizophrenia than in those who did not. Prominent among these signs were hypoactivity, rigidity, speech abnormalities, abnormal gait, and poor coordination. In a 30-year follow-up study (59) a higher rate of difficulty in learning to walk was noted in preschizophrenic subjects.

These results indicate that a higher rate of neurological abnormalities characterizes a portion of the offspring and relatives of schizophrenic patients who would be assumed to be at higher risk to develop schizophrenia on a genetic basis. In some of these studies the nature of the abnormalities clearly resembles those commonly seen in adolescent and adult schizophrenic samples, namely, problems in coordination, motor dysfunction, and sensory integration. This is compatible with the view that neurological signs reflect a familially transmitted alteration in neurological processes that constitutes a vulnerability or diathesis to subsequent schizophrenia. Whether neurological signs are specific to familial schizophrenia, however, requires further study, as the relationship between neurological signs and other possible etiologic factors has not been adequately explored.

DISCUSSION

In light of the available evidence, how promising is the study of abnormal neurological signs in schizophrenia? In spite of some methodological limitations, the evidence for a higher rate of neurological abnormalities in schizophrenia is consistent and compelling. These signs are not random but are concentrated in the functional domains of sensory integration, coordination, and sequential motor acts. There is some suggestion that these functional systems are impaired at the level of subcortical structures such as the limbic system. Furthermore, there are indications that neurological signs are not equally likely to occur among all schizophrenic patients but are more prominent among those with thought disorder and cognitive impairments, as well as those with chronic forms of the illness. In addition, there is significant reason to believe that neurological abnormalities characterize a portion of the relatives of schizophrenic patients and predate the onset of the schizophrenic illness. They may also be more likely to appear in those with a family history of schizophrenia. Less clear are possible relationships with other variables such as negative symptoms, premorbid functioning, age at onset, and duration of illness.

It is critical to bear in mind that with very few exceptions these studies have not been designed to elaborate the meaning of neurological signs in terms of neuroanatomical or functional localization on the one hand, and relationships to putative schizophrenic subgroups on the other. The progress to date on this question has derived almost exclusively from post hoc analyses. Failures to replicate often came from studies with limited power to find such relationships, if replication had been attempted at all. In this light, the positive findings to date are encouraging indeed. There certainly is no basis for dismissing neurological signs as in principle nonspecific or soft. Abnormal signs in neurology have traditionally been assumed to be highly informative about the nature and location of disease once the significance of these signs is understood. There is no reason to assume that this is different in the case of schizophrenia.

However, for these signs to be optimally informative, a more rigorous and systematic program of research will be needed. The following is a suggested blueprint for such work. First, a structured and reliable procedure for rating those neurological signs common in schizophrenia must be developed. Then that battery can be used to establish the temporal stability of neurological signs and to determine the influence of variables such as age, sex, clinical state, and medication. In larger samples, conceptually meaningful groupings and empirically derived factors of signs can be identified and explored. The resulting dimensions of neurological impairment can then be examined in relationship to known risk factors (e.g., perinatal insult, family history, season of birth), clinical characteristics (e.g., age at onset, premorbid functioning, paranoid subtype, negative symptoms, cognitive impairment, treatment response, chronicity), and other neurodiagnostic procedures (CAT scan, evoked potentials, PET scan, neuropsychological tests). For example, a systematic effort to relate neurological signs to the more intensive and technologically sophisticated procedures could, on the one hand, help to clarify the neuroanatomical significance of neurological signs. This approach has recently been employed to good advantage in relating neurological signs to PET scan findings in Huntington's disease (60). Conversely, neurological signs could be used as an inexpensive way to identify subjects most likely to yield valuable results in studies of small samples with expensive, technologically complex procedures. For example, if an investigator were in a position to obtain PET scans on a small number of patients and were interested in the hypothesis that a subgroup of schizophrenic patients demonstrated relative hypofrontality of glucose utilization (61), the investigator's chances might be improved if he or she chose subjects who showed impairments in sequencing motor acts. Of course, further work would then be required to assess the generalizability of the results to other schizophrenic subgroups.

Compared to other techniques for evaluating neurological aspects of schizophrenia, the study of neurological signs is inexpensive and can be readily employed with large samples. Properly designed investigations are likely to establish the meaning and utility of neurological signs in the study of schizophrenia. Robust relationships could be readily applied in a wide range of clinical settings. This considerable promise, weighed against the rather modest cost of further work in this area, argues strongly that it should be pursued.

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High Users of Outpatient Mental Health Services, I: Definition and Characteristics

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Mental health coverage generally limits benefits for high use, which is assumed to be discretionary. The authors present data from the National Medical Care Utilization and Expenditure Survey. Of the individuals who made mental health outpatient visits in 1980, 9.4% made 25 or more visits and accounted for 50% of mental health visits and expenditures. These high users were compared with low users and with high users of other health care. One-third of the mental health high users were highly disabled and had multiple medical disorders. The authors point out the heterogeneity of this population and suggest that psychiatric benefits be differentiated according to patients' needs and services offered.

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The fact that a small proportion of users consume a disproportionate share of medical services has long been recognized (1–6). Insurers are concerned that some of the care used by the group of persistent users may not be necessary. Such persons are very costly. Most know they have chronic conditions. Anticipating that they will require care, they seek insurance plans with favorable coverage for their conditions (adverse selection). There is also a presumption that some of these persons exacerbate their needs through poor personal habits (3). Insurers would like to control use to reduce costs, minimize adverse selection, change self-injurious behavior, and adjust the premiums for beneficiaries at high risk.

Mental illness is usually cited as one of the common conditions of persons who use medical services repeatedly. Length of stay norms for mental disorders are difficult to establish, leading to the presumption of a higher proportion of unnecessary hospitalizations or more days of stay. Some outpatient mental health care is viewed as discretionary or medically unnecessary (used for self-actualization or self-awareness). Practice style historically has been considered to be much more important in the treatment of mental disorders than in other health care, given the lack of consensus on defined treatment regimens for specific disorders. Only recently has such questioning in the health arena been considered with the same concern (7).

The result has been that, although health insurance packages have included catastrophic coverage to protect the higher user, mental health coverage has been characterized by benefit limits on high use, which are based on the assumption that high use is discretionary at best or unnecessary. In this paper we present an analysis of the high user of outpatient mental health services, compare high users of other health services with high users of mental health services, and seek to differentiate the high mental health users into subgroups as a prerequisite for more sophisticated options for insuring such care. These options are discussed in more detail in "High Users of Outpatient Mental Health Services, II: Implications for Practice and Policy," which follows this article.

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DATA SOURCE

Data from the National Medical Care Utilization and Expenditure Survey made possible a description of the annual use of outpatient care by the U.S. population and a comparison of the use for mental disorders to that for other conditions. These data enabled us to examine patterns of use in a single year, 1980. The National Medical Care Utilization and Expenditure Survey was designed to provide estimates of the health of the civilian noninstitutionalized population of the United States, its utilization of and expenditures for various types of medical care, its health insurance coverage, and the amounts paid by insurance companies for health care. About 17,900 persons were included in the national household sample; of these, 715 had seen a psychiatrist or psychologist or had otherwise had at least one "mental health visit" during the year. The data for all the tables in this article were inflated to the U.S. population.

The statistics in this article are based on a sample of the population rather than the entire population. Thus, these data may differ from values that would be obtained from a complete census. The standard errors used in assessing the significance of the statistics were estimated by using the "Standard Errors Program for Computing Standardized Rates for Sample Survey Data," developed by Shah (8).

The Health Care Financing Administration and the National Center for Health Statistics cosponsored the survey. The data were collected by the Research Triangle Institute, National Opinion Research Center, and SysteMetrics, Inc., under contract to the U.S. Department of Health and Human Services. Detailed descriptions of the survey have been published (9).

A mental health visit was defined as any visit for which a mental health condition was given as the reason (regardless of the provider type or setting) or any visit to a psychiatrist, psychologist, or a psychiatric clinic (regardless of whether there was a mental health reason for the visit). This definition of mental health condition may be viewed as conservative because only specific mental disorders were included. If reports of "nerves" were included, the number of mental conditions would increase by almost 50%. Further, although the number of mental health visits from the National Medical Care Utilization and Expenditure Survey was higher than the numbers from prior surveys (10), mental health conditions were probably still underreported.

THE HIGH USER POPULATION

Seventy percent of the sample surveyed had at least one health visit during the year. For the persons who had such visits, the average number of visits per person was 4.7 per year. For mental health visits, on the other hand, use was low; only 4.3% of the sample reported one or more mental health visits during the year. For that proportion of the sample, however, the average number of visits per year was higher than for health visits—8.2 mental health visits per user.

TABLE 1. Number of Visits of Persons Who Made Health or Mental Health Visits in 1980[a]

Number of Visits	Persons With Health Visits Other Than Mental Health Visits (N=177,723,601)		Persons With Mental Health Visits (N=9,574,660)	
	%	Cumulative %	%	Cumulative %
1	22.23	22.23	34.68	34.68
2	16.37	38.60	14.15	48.83
3	12.35	50.95	8.57	57.40
4	9.80	60.75	4.79	62.19
5	6.94	67.69	4.00	66.19
6	5.54	73.23	2.69	68.88
7	4.08	77.31	2.81	71.70
8	3.38	80.69	2.17	73.87
9	2.81	83.50	2.35	76.22
10	2.40	85.90	1.57	77.79
11	1.98	87.88	3.05	80.84
12	1.75	89.63	1.90	82.74
13	1.34	90.97	0.81	83.56
14	1.04	92.02	0.92	84.48
15–24	4.89	96.90	5.68	90.15
25–49	2.44	99.34	7.81	97.97
≥50	0.66	100.00	2.03	100.00

[a] Data from the National Medical Care Utilization and Expenditure Survey.

Table 1 shows the distribution of persons by number of visits for all visits other than those for mental health reasons and for mental health visits. Distributions were similar: there were high proportions of persons with one, two, or three visits, gradual drop-offs in the number of persons as the number of visits increased from four to 10, and then small concentrations of high users who had over 14 visits per year.

There were significant differences in the proportions at the two extremes of the distributions for health visits and mental health visits, however. For persons with mental health visits, 34.7% had only one visit and 57.4% had three or fewer visits. For persons with health visits, 22.2% had only one visit and 51.0% had three or fewer visits. At the other extreme, 15.5% of the persons with mental health visits had 15 or more visits, while for persons with health visits the proportion was 8.0%. The proportion of persons in each of the visit categories 10–14, 15–24, 25–49, and ≥50 was higher for mental health than for health visits, especially in the 25–49-visit category. Because of the higher percentage of persons with one to three visits, the median number of visits for mental health (just over two visits) was lower than for health (just under 3 visits). The higher proportions of persons in the high-visit categories for mental health, on the other hand, caused the mean number of visits per user to be higher for mental health than for general health (table 1).

Comparison of one class of disorders, mental disorders with all other classes of health conditions is not as informative as comparison with specific health conditions. Eight conditions were selected for comparison in

TABLE 2. Number of Visits of Persons Who Made Visits for Selected Medical Conditions in 1980[a]

Medical Condition Given as Reason for Visit	Percent of Persons With Condition					
	All Persons	1–9 Visits	10–14 Visits	15–24 Visits	25–49 Visits	≥50 Visits
All conditions	100.0	74.0	12.5	8.0	4.4	1.2
All conditions except mental disorders	100.0	83.5	8.5	4.9	2.4	0.7
Mental disorders	100.0	74.3	10.6	5.8	7.5	1.9
Selected other conditions						
Endocrine/metabolic disorders	100.0	88.9	6.0	3.3	1.7	0.3
Hypertension	100.0	94.2	3.4	1.7	0.6	0.1
Atherosclerotic cardiovascular disease	100.0	85.3	7.0	3.1	2.5	2.1
Respiratory conditions	100.0	95.8	1.8	1.4	1.0	0.1
Digestive disorders	100.0	97.7	1.7	0.6	0.0	0.0
Musculoskeletal conditions	100.0	88.2	4.6	3.8	2.8	0.6
Ill-determined signs and symptoms	100.0	96.0	1.9	0.8	1.1	0.3
Skin conditions	100.0	97.1	1.7	0.5	0.7	0.1

[a]Data from the National Medical Care Utilization and Expenditure Survey.

this analysis. Four were chosen because they represent chronic conditions that potentially require high levels of outpatient care: endocrine and metabolic disorders, hypertension, atherosclerotic cardiovascular disease, and respiratory conditions other than upper respiratory tract conditions. Three were chosen because they were more likely to be psychosomatic or to mask psychiatric illness: digestive disorders, musculoskeletal conditions, and ill-determined signs and symptoms. Finally, skin conditions were selected because they receive more discretionary care than other disorders.

The distribution of visits for the eight medical conditions and for mental disorders is shown in table 2. Visits for hypertension, a health condition with the same prevalence (20%) as mental disorder (11), showed a different pattern: 94.2% of the patients with visits for hypertension had 1–9 yearly visits, and only 0.1% had 50 or more visits per year. The distribution of visits for persons with visits for atherosclerotic cardiovascular disease seemed most similar to that for persons with mental disorder visits. The major difference remained in the 25–49-visit category, where there was a significantly higher percentage for persons with mental disorder visits than for persons with visits for atherosclerotic cardiovascular disease (7.5% versus 2.5%). The distribution of persons with visits for endocrine/metabolic disorders and musculoskeletal conditions was also similar but also without the bulge at the 25–49-visit category. The distribution of persons by visit categories for all disorders except mental illness illustrates the change when visits for all conditions are tallied rather than broken down by disorder. Since many people have visits for more than one condition during the year, the proportion in the 1–9-visit category is considerably lower than when each condition is looked at separately.

Proportion of Resources Used

TABLE 3. Percent of 1980 Visits and Expenditures for Outpatient Services Accounted for by High Users With Selected Medical Conditions[a]

Medical Condition Given as Reason for Visit	High Users (≥25 Visits)		
	% of Persons With Condition	% of Visits	% of Expenses for Outpatient Services
All conditions	5.6	26.0	22.5
All conditions except mental disorders	3.1	22.3	18.7
Mental disorders	9.4	50.3	49.2
Selected other conditions			
Endocrine/metabolic disorders	2.0	20.7	14.9
Hypertension	0.7	7.9	2.5
Atherosclerotic cardiovascular disease	4.6	41.0	24.8
Respiratory conditions	1.1	14.5	6.5
Digestive disorders	0.0	0.0	0.0
Musculoskeletal conditions	3.4	28.4	21.2
Ill-determined signs and symptoms	1.4	0.0	15.0
Skin conditions	0.8	10.4	8.0

[a]Data from the National Medical Care Utilization and Expenditure Survey.

Another way to examine the distribution of visits is to look at the proportion of outpatient resources used by high users. If "high users" are defined as persons with 25 or more annual visits for each disorder or condition, then one can look at the total visits and expenditures for outpatient visits for each condition accounted for by high users. Table 3 illustrates this type of analysis. Three patterns emerge. First, some conditions, such as hypertension, had few high users (0.7%), and these high users accounted for a disproportionate percentage of visits (7.9%) and an intermediate proportion of expenditures for that condition (2.5%). Endocrine disorders, skin conditions, ill-determined signs and symptoms, and respiratory conditions all follow this pattern.

Atherosclerotic cardiovascular disease and musculoskeletal conditions formed a second pattern, which is characterized by a higher proportion of high users (3%–5%), who accounted for a considerably higher proportion of visits and an intermediate proportion of

TABLE 4. Characteristics of High and Low Users of Outpatient Health and Mental Health Services in 1980[a]

	Health Services		Mental Health Services	
Characteristic	High Users	Low Users	High Users	Low Users
Demographic				
Age (mean years)	52.4	65.6[b]	36.8[c]	46.2[b]
Family income (dollars)	21,900	25,060[b]	24,670	24,520
High school graduate (%)	66	68	81[c]	72
White (%)	87	88	93[c]	93
Married (%)	63	61	45[c]	57
Employed (%)	51	69[b]	76[c]	69
Eligible for Medicaid all year (%)	19	10[b]	22	15
Had commercial insurance all year (%)	82	82	74	80
Health				
Medical conditions (mean number)	7.3	3.6[b]	5.7[c]	5.8
Duration of restricted activity (mean days)	75.9	17.3[b]	28.4[c]	29.7
Time in bed (mean days)	29.8	6.1[b]	11.0[c]	11.2
Time off work (mean days)	18.0	30.0[b]	7.0[c]	13.5
Time in the hospital (mean nights)	8.8	1.7[b]	5.1	2.7

[a] Persons aged 18 or older. High user defined as person who made 25 or more visits per year. Data from the National Medical Care Utilization and Expenditure Survey.

[b] Significantly different from value for high users ($p<.05$).

[c] Significantly different from value for high users of health care ($p<.05$).

total expenditures for that condition. The fact that the proportion of expenditures was lower than the proportion of visits for the high users in the first two types or groups of conditions is presumably due to decreasing cost per visit as the number of visits increased. Such a pattern would be expected if the initial visits were for new patients who received complete checkups and subsequent visits were for established patients for periodic checkups or if some initial visits for that year were for established patients from a prior year who were receiving periodic checkups.

Mental conditions represented a third type of use pattern and were unique in two ways: first, the proportion of high users was double that of any other condition under comparison here; second, the percentage of expenditures accounted for by the high users was high, almost the same as the percentage of visits—indicating that there is no decline in the cost per visit as the number of annual visits increases. This is due largely to consistent fees for visits throughout an episode of outpatient care and partially to the relatively small cost of ancillary services in psychiatric outpatient care, with the resultant cost being largely labor cost.

Fewer than 10% of the users of outpatient mental health care accounted for nearly 50% of the mental health expenditures. Users of mental health services accounted for 15.4% of the total outpatient expenditures for all high users of health care but only 4.0% of the total expenditures for low users and 6.5% of the total expenditures for all users.

Comparing High and Low Health and Mental Health Users

For the purposes of this analysis, the 90th percentile was used to define a "high user." Persons with more than 12 health visits or more than 24 mental health visits were considered high users. While the data from this national survey did not enable us to differentiate cases by mental disorder diagnosis or by severity of symptoms, they did permit analysis of sociodemographic, economic, and service utilization variables for the high-use sample and comparisons with the low-use mental health group and with the high and low health users. Table 4 compares the high and low users of outpatient health and mental health care on selected characteristics. The high users of mental health care were younger but were not significantly different from the mental health care low users on other demographic, health status, or insurance variables. This is in contrast to the comparison of the high and low health care users. Compared to the low health care users, the high users of health care were significantly younger and poorer, more of them were unemployed and eligible for Medicaid, and they had more medical conditions and days on which their activities were restricted or they were in bed or in the hospital. The high users of mental health care were younger and better educated than the high health care users, and more of them were white, employed, and unmarried. The high mental health care users had fewer medical conditions and fewer days on which their activities were restricted or they were in bed.

Differentiating High Users of Mental Health Services

We sought to further differentiate empirically the high users of mental health services, who accounted for fewer than 10% of those who made visits for mental disorders but 50% of the mental disorder visits and costs. Given the concern that the high user group in mental health could be composed largely of persons without a real medical need for care, it is important to describe this group further. This group was not clinically homogeneous but consisted of many subgroups, including persons with serious mental disorders who were receiving long-term psychotherapy, persons with chronic mental disorders who were receiving a mix of maintenance drug treatment and supportive therapy, persons with multiple somatic as well as mental conditions, and persons less seriously ill who were undergoing various forms of insight-oriented psychotherapy.

Using direct measures of health status and disability, we divided the high users of mental health services into two groups: those with high disability (low health status) and those with low disability (high health status). On an a priori basis, persons were placed in the high-disability group if they had any one of the following characteristics: 1) under age 65 and eligible for Medicare by virtue of a disability, 2) more than seven health conditions (the 75th percentile), 3) perceived health care status of fair or poor, or 4) limited in activity. This dichotomization of the persons wth 25 or more mental health visits resulted in 635,000 high users in the low-disability group and 308,000 in the high-disability group. These two groups were then compared, as shown in table 5. The high-disability group had significantly higher values on all measures of service use, restrictions and limitations, and health status measures. For example, the high-disability group had an average of 20.6 days in bed per year and the low-disability group had 3.6 days per year.

Clearly, therefore, no matter how gross these indicators are, the high-use mental health group does not seem to be composed exclusively of the stereotypical healthy patient in long-term treatment. At least one-third of this group is a population with multiple health problems in addition to their mental health conditions. Further, the high-use group varies in the primary setting in which the majority of their visits occurred; 39% were primarily seen in psychiatrists' offices, 40% in psychologists' offices, 18% in the offices of other providers (physicians, social workers, counselors), and 3% in organized care settings.

POLICY IMPLICATIONS

The design of benefits for outpatient psychiatric treatment has focused on limits on excessive use, presumed to be due to moral hazard. It may be inferred that benefits for outpatient psychiatric services have been limited on the assumption that such services are discretionary and subject to overuse when their effective price is lowered by insurance. It seems to us that this assumption derives from the stereotype characterizing all outpatient psychiatric care as long-term psychotherapy for the personal growth of relatively healthy individuals and not from a determination regarding medically necessary services. As we have discussed, outpatient mental health services and the individuals who use them are more diverse than the stereotype.

TABLE 5. Characteristics of High Users of Outpatient Mental Health Services With Low or High Disability in 1980[a]

	Persons With ≥25 Mental Health Visits	
Characteristic	Low Disability (N=635,000)	High Disability (N=308,000)
Utilization		
Hospital discharges (mean number)	0.06	0.73
Visits other than for mental disorders (mean number)	5.7	15.2
Health		
Time in bed (mean days)	3.6	20.6
Duration of restricted activity (mean days)	11.5	38.4
Medical conditions (mean number)	3.7	7.7
Extent of activity limitation (mean score)[b]	3.7	2.7
Perceived health status (mean score)[c]	1.8	2.5
Demographic		
Female (%)	56	55
Age (mean years)	29	33

[a] Data from the National Medical Care Utilization and Expenditure Survey. See text for definition of high disability.
[b] Range=1–4, 1=most limited.
[c] Range=1–4, 4=poorest.

The findings of our study underscore the heterogeneity of the population of high users of outpatient mental health services. The stereotype of the healthy, high-functioning patient receiving long-term psychotherapy as the high user is not entirely correct. Although one cannot deny the presence of a substantial number of such patients, it is now clear that nearly one-third of the high-user group have at least one measure of significant disability. From a policy perspective, these findings suggest that psychiatric benefit limits ought to be differentiated as much as possible according to the heterogeneous needs of patients and ought to be as specific as the types of services offered to them.

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High Users of Outpatient Mental Health Services, II: Implications for Practice and Policy

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Four assumptions underlie the stereotyped view of use of outpatient mental health services: 1) all use is alike, 2) any use leads to high use, 3) all high use is discretionary, and 4) insurance encourages excessive use. The authors refute the first three assumptions and suggest that different types of treatment episodes vary in their responsiveness to price. Diagnosis appears to be a poor indicator of inpatient needs; some coverage limits outpatient benefits according to type of treatment. The authors favor a combination of pricing strategies, as well as case management and clinical review for high users, which would not impede initial treatment but would limit excessive use of mental health services.

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Controlling the costs associated with excessive use of outpatient mental health services has been a preoccupation of those who pay for psychiatric services. Psychiatric benefits have been limited on the assumption that mental health services are discretionary and subject to overuse when the effective price of the service is lowered by insurance. This is referred to as "moral hazard." The moral hazard assumption derives from the stereotype characterizing all outpatient psychiatric care as long-term psychotherapy for the personal growth of relatively healthy individuals and not as medically necessary services. This stereotype ignores the diversity of outpatient mental health services and the individuals who use them.

Data on high users of outpatient mental health services, such as the findings presented by Taube et al. in the preceding paper, support the heterogeneity of outpatient mental health services and have several important implications for policy and practice.

Although 50% of the expenditures for outpatient mental health services are consumed by the 10% of users who exceed 24 visits per year, the median number of visits for all users is only two visits, and approximately one-third of the high users have some evidence of disability or need for care other than a recorded diagnosis of mental disorder (Taube et al.). Visit and dollar limits, often coupled with substantial copayments, usually affect all psychiatric patients without differentiating the disabled from the disenchanted and without distinguishing medication maintenance from psychotherapy. Informed benefit design would attempt to differentiate discretionary from medically necessary care on the basis of criteria other than diagnosis.

In this paper we examine the implications of the

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findings from research on high users of outpatient mental health services for benefit design and financing policy. We propose to distinguish fact from fantasy, recommend alternatives to existing financing mechanisms, and suggest avenues for future research.

STEREOTYPES

Four linked assumptions underlie the stereotyped view of the use of outpatient psychiatric services: 1) all use is alike, 2) any use leads to high use, 3) all high use is discretionary and therefore excessive, and 4) insurance encourages excessive use. We will discuss each assumption and stereotype.

Historically, the insurance industry has adopted a stereotype of psychiatric treatment as discretionary, ill-defined, and interminable. This stereotype was reinforced by treatment practices in the community and in academic professional circles. Although other forms of treatment existed, long-term hospital care and extended psychoanalytic outpatient treatment dominated mental health practice, especially from the 1940s into the early 1960s. This period coincided with the most rapid growth of insurance for health care. It is perhaps understandable that the insurance benefits which developed during this period reflected the stereotypes of the times and made no important distinctions between types of psychiatric procedures or episodes of care (1). From the perspective of the insurance industry, a restriction placed on the outpatient treatment of mental disorders was a limitation placed on discretionary, interminable treatments of questionable value, great cost, and considerable stigma. Furthermore, catastrophic protection was considered unnecessary; a large system of public hospitals was available for individuals who exhausted private resources for psychiatric services.

Insurance coverage of inpatient and outpatient mental health services historically has been limited primarily on the basis of diagnosis and only secondarily on the basis of type of care provided. Medicare coverage of outpatient physician services for "nervous and mental disorders" is perhaps the prototype for such limitations. This pattern of limitation differs from insurance benefits for the majority of general health services; few coverage limitations are based on diagnosis alone (maternity, dental, and AIDS coverage restrictions are exceptions). Restrictions are sometimes placed on the availability of specific surgical procedures, on the frequency of selected diagnostic tests, or on the number and frequency of office visits without reference to diagnosis. In contrast, a patient with a mental disorder may be denied insurance coverage for treatment regardless of need—whether the service provided is a hospital stay to prevent a suicide or to enhance the emotional maturity of an errant teenager; whether it is an admission to evaluate an elderly patient for a treatable cause of a psychotic dementia or to provide a safe and separate environment for long-term psychotherapy, regression, and personal development; and whether it is a course of brief (perhaps no more than six) outpatient visits of short duration (30 minutes) to solve an immediate crisis or a complete psychoanalysis requiring four visits per week for 3 or 4 years. Limitations on insurance coverage of mental health care have generally ignored such differences in the types of treatments and treatment episodes in favor of global restrictions for the entire class of mental disorders and their associated treatment.

Limits based on diagnosis alone are based on the assumption that all utilization of outpatient mental health services follows the same pattern. The data (Taube et al.), however, suggest that the patterns of use are diverse. Within certain limits, some use does not always lead to high use and the use of some outpatient services appears to follow need (2, 3).

It is evident that the first three assumptions which shape the stereotype are incorrect: clinically, we know that all use is not alike. Many different patterns of use (such as the examples given) are associated with the care and treatment of a wide array of patients and their diverse problems. All use does not lead to high use. About half of all psychiatric outpatients have at most two visits during a year. And not all high users are discretionary users. National data (Taube et al.) indicate that at least one-third of the high users of mental health services have some form of serious disability. The concern for the policy maker, then, ought to be to distinguish necessary from discretionary and excessive use.

According to the theory of insurance benefit design, insurance coverage ought to be structured to provide adequate economic support for necessary treatment and protection against financial catastrophes beyond the control of the beneficiary. It must also reflect appropriate concerns about moral hazard (1, 4). To complete the analysis of the stereotype of outpatient mental health utilization it is useful to examine more closely the fourth assumption, concerning the effect of insurance coverage on use of services.

MORAL HAZARD

Most of the literature on the price-responsiveness of the demand for outpatient psychiatric services indicates that demand for these services is more elastic than the demand for outpatient general health care (5–8). In other words, most research on this question indicates that the use of outpatient mental health services is more sensitive to changes in the price of care, especially as it is affected by the design of insurance benefits. Increases in the price of services paid by patients (such as copayments) result in a decrease in utilization. The Health Insurance Experiment conducted by the Rand Corporation (9) also demonstrated that the use of mental health services is sensitive to price, although initially the authors concluded that outpatient mental health use is not significantly more price-sensitive than general health service use. Recent modifications in their analysis (10) suggest that they may have underestimated the price-responsiveness of outpatient mental health services.

All of the studies of demand for outpatient mental health services have examined annual use, aggregating a wide variety of psychiatric services into a single dependent variable, treating outpatient psychiatric care as a homogeneous commodity. None of the studies of the demand for outpatient mental health services has differentiated between different types of services, which reflect different patient needs. The Rand Corporation Health Insurance Experiment (9), however, attempted to measure patient need and found that service use was directly related to the measure of need. Other research also supports this conclusion (Knesper et al., unpublished data, 1986). Research on this issue is in its infancy, but many investigators believe it is desirable to differentiate between the various types of outpatient treatment and to identify the patient needs that determine service choice and use. This level of analysis is especially important if economic research is to inform policy on insurance benefit design.

An analysis of the demand for various types of clinical services or episodes of psychiatric care could determine if the responsiveness of demand to price (and hence, the potential for moral hazard) varies for different patient populations and across specialized services. If mental health services are not homogeneous, then it seems reasonable to assume that some types of services and treatment episodes demonstrate moral hazard and others do not, conforming to the pattern seen for medically necessary and less discretionary care. For example, one might predict that episodes of outpatient care associated with an episode of inpatient care are less responsive to price than episodes without a hospitalization, especially if the hospital care was determined by clinical review to have been necessary. The same might be assumed for episodes of outpatient care in which antipsychotic or antidepressant medication is prescribed or for short office visits for "medical management." In addition, it seems likely that weekly psychotherapy would be less responsive to changes in price than intensive psychotherapy.

The real challenge for the mental health field is to examine types and patterns of practice more carefully to distinguish discretionary from medically necessary treatment. The goal is to define acceptable practice and acceptable variations in practice so that payment policy accommodates and enhances access to needed care and treatment. This is a problem for financing policy guided by an understanding of the demand for services, such as insurance reimbursements, and for "supply-side" policies, such as prospective payment. In both cases the needs of patients must be balanced against the desire to control costs equitably. At the present time this is extremely difficult to accomplish. Research findings on the efficacy of brief treatment strategies and pharmacotherapy are not universally incorporated into clinical practice; there is resistance to change and even to documenting and compiling effective treatments (viz., the debate over the American Psychiatric Association book on psychiatric therapies). The great fear seems to be that standardizing treatments will limit an individual therapist's interventions with an individual patient. The fear seems to center on concerns about whether or not a particular practice will be considered medically necessary and subject to insurance coverage. In the absence of a consensus on medical necessity, one could define the concept operationally, in terms of the propensity of the type of care or practice to moral hazard. After all, it is fear of moral hazard in part that motivates consideration of medical necessity and the labeling of some treatment as discretionary.

ALTERNATIVE POLICIES AND FUTURE RESEARCH

To define "medical necessity" operationally in terms of moral hazard requires further development of a new area of health economics research.

Basic economic theory suggests that demand for less discretionary care is less elastic (i.e., use is less responsive to price or income). The proposition can be tested in an analysis of demand, on the one hand revealing treatment episodes that account for the dramatic price-responsiveness of outpatient mental health services in the aggregate and on the other hand identifying treatment episodes for which the pattern of demand is similar to the elasticities reported for general health care. The results of such an analysis would help to differentiate those services and treatment episodes which ought to be financed according to the same benefit design as that for general health services, distinguishing them from those services which suggest a different design.

In addition to informing benefit design for the purpose of cost containment, data on income and price elasticity contribute to our knowledge of access to care and equitable distribution of resources. If income and price are significant barriers to access to services that are regarded as essential, then economic barriers might be lifted (in spite of increased cost). On the other hand, if some types of episodes (e.g., long-term outpatient care) are used by only one sector of the population (e.g., those with incomes over $40,000), then insurance coverage might only serve to redistribute resources inequitably, from nonusers (those with incomes less than $40,000) to users (those with higher incomes). These important policy questions can only be addressed with necessary precision by refining the state of the art of economic research on demand.

Research of this type is under way. Preliminary models have been developed to examine price and income elasticity in outpatient services, identifying different types of care and different patterns or episodes of psychiatric care (11). Some work on large data sets has been funded by the National Institute of Mental Health and reported at a recent conference (12, 13).

Beyond Diagnosis

Traditionally, diagnosis has been used to define medical necessity or at least to suggest what kinds of care should be subject to what kind of financing. Currently, this approach is best exemplified by the use of diagnosis-related groups to adjust prospective payments for services to fit the needs of specified groups of patients. Diagnosis does not work particularly well for defining the inpatient needs of medical patients (14); it performs somewhat less well for psychiatric patients (15–17, summary of other work in 18). The limitations of diagnosis for reimbursements for outpatient mental health services have been discussed by Sharfstein et al. (19) and earlier in this article.

Some reimbursement policies already recognize the need to move beyond diagnosis in defining benefit limits. The United Auto Workers policies place limits on psychotherapy specifically, as does Medicare. An attempt has been made to fit reimbursement to clinical practice and still control costs on the basis of certain assumptions about moral hazard. Pending the results of the demand studies we have described, these assumptions continue to guide benefit design.

This philosophy of benefit design was employed when the Medicare part B outpatient psychiatric benefit was modified for patients with Alzheimer's disease and related organic mental disorders (20). The new reimbursement guidelines distinguish between office visits for medical management and those for psychotherapy. For patients with Alzheimer's disease, office visits for medical management are reimbursed on a par with the outpatient care of nonpsychiatric patients, whereas office visits billed as psychotherapy are subject to the $500 (with 50% copayment) limit for the outpatient treatment of patients with mental disorders. A detailed discussion of this policy and its implications are reported elsewhere (21) and are beyond the scope of this paper. This example illustrates the need to move beyond stereotypes to information about the diversity of patients and their utilization of services when designing insurance benefits for psychiatric care.

CAVEATS AND CONCLUSIONS

Reimbursement based on specific procedures, episodes, and patterns of psychiatric care is no panacea. There are legitimate concerns that it is too difficult to define "medical necessity," even in terms of propensity for moral hazard, or that such an approach gives too much consideration to the costs of care. Recent data from the Rand Health Insurance Experiment suggest that changes in demand in response to cost sharing affect utilization of medically effective and ineffective care equally (22). Furthermore, insurance is designed to increase access equitably.

A field that prides itself on concern for individual differences between patients naturally is suspicious of standardization and classification. Yet these processes are common in medicine generally, and conformity with medical practice serves as a rationale for continued coverage of psychiatric services under medical insurance and health care financing mechanisms. Some may fear that their type of practice will not be regarded as medically necessary. Certainly, psychotherapists express concern that the recent change in Medicare which differentiates medical management from psychotherapy undermines the reimbursement of their practice. Although it is possible that the psychotherapy benefit could be more vulnerable to change or elimination if it is distinguished from other psychiatric services, psychotherapy has been the principal service covered by insurance policies for several decades and there is no reason to suspect that there has been a decline in the demand for it. Furthermore, removing medical management from the benefit limitation effectively increases the benefit for psychotherapy.

The most efficient mechanism to control costs would focus on the high user of services, the 10% of users who make more than 24 visits per year and account for 50% of total expenditures. This suggests careful consideration of the medical necessity of such care. Separating the types of service and paying for them differently may accomplish this objective.

Changes in pricing strategies are not the only effective method for controlling high use. The pattern of use reported here and in the preceding article suggests the potential efficiency of a focused program of case management and clinical review of the 10% of cases approaching the 24-visit level. Rather than limiting shorter episodes of care with high deductibles and steep initial copayments, focusing on the high user could more efficiently control the most expensive use, distinguishing necessary from inappropriate or noncritical care. A combination of clinical review and authorization for treatment beyond 20 visits is used by some insurers. Some couple clinical review with an increase in patient cost sharing by raising the copayments for care beyond a specified limit.

A policy that presents few financial barriers to initiating treatment but limits excessive use could control costs responsibly and increase the access to care for the large proportion of the population who have mental disorders but do not use any mental health services (23). There seems little justification for impeding the initial use of outpatient mental health services, given that 50% of the users make only two visits in a year and that the 90% of users who make fewer than 25 visits account for only about half of the expenditures.

A policy that encourages necessary use and controls moral hazard satisfies insurance principles and promotes public health. Ultimately, the question in insurance policy is not what is appropriate treatment but what kind of treatments are appropriate for everyone to pay for (through premiums or taxes) even though only some will use them. Public willingness is linked to perceptions of efficacy and concerns about moral hazard. Concerns about moral hazard and the appropriateness of insurance coverage apply to many services, not just mental health care. Cosmetic surgery, dental and vision care, maternity care, and certain other "elective" procedures are all subject to the same concerns. The success of financing policy is measured by its ability to equitably distribute scarce resources by distinguishing necessary from unnecessary care. The rules should not be arbitrary; they should be fair to patients, providers, and payers. This can only be accomplished when the same principles of insurance and public health apply to the financing of mental health care as to general health care.

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Mental Patients' Attitudes Toward Hospitalization: A Neglected Aspect of Hospital Tenure

Robert E. Drake, M.D., Ph.D., and Michael A. Wallach, Ph.D.

Recent research on hospital tenure has neglected mental patients' attitudes toward hospitalization. The authors consider problems with past research on these attitudes and examine "living preference"—the patient's preference for living in the hospital or the community. Assessments of patients' living preferences were obtained from clinicians working with 187 chronically mentally ill patients in a state hospital aftercare program. These assessments strongly predicted both components of hospital tenure—rehospitalization and in-hospital days—during a 1-year follow-up. The authors point out the conceptual, heuristic, and practical clinical advantages of examining living preference rather than traditional correlates of hospital tenure.

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Hospital tenure refers to patients' tendency to use psychiatric hospitalization. Measured as readmission rate, length of stay, or in-hospital days over a set follow-up period, hospital tenure is the most frequently used outcome measure in the treatment of the chronically mentally ill. Recently, evidence that long-term hospitalization is not helpful for chronic mental patients (1) and pressures to decrease costs and to design a system of prospective payments (2) have spurred a renewal of interest in hospital tenure. Despite obvious limitations (3), hospital tenure has face validity and clear financial implications and affects prognosis in the sense that hospitalization tends to predict further hospitalization (4).

For the chronically mentally ill, hospital tenure is usually viewed in relation to diagnosis (5), symptoms of psychopathology (6), hospitalization history (5), personality defects (7), institutional policies (8), functional skills (9), familial living environment (10), and community treatment (11). Relatively ignored are patients' attitudes toward hospitalization. For example, in a 1985 survey of factors deemed to influence length of hospital stay (2), mental health professionals neglected patients' attitudes completely. Chronic mental patients are sometimes viewed as too disorganized to behave effectively in congruence with their expressed attitudes (12)—a view that may explain the neglect of patients' attitudes (13). Attitude research has seemed to support this outlook by failing to demonstrate a strong relationship between attitudes and hospital tenure (14). Nevertheless, the patient's subjective view of the hospital seems to be an important perspective. Taking the patient's phenomenology into account may explain how a variety of risk factors and supports are idiosyncratically perceived and weighted to arrive at their meaning for the given patient.

The failure to establish a relationship between attitudes and hospitalization may have occurred because traditional attitude measures assess general attitudes (e.g., favorableness toward the hospital) rather than attitudes toward performing a specific act (e.g., living in the hospital versus receiving treatment there). They also fail to take into account the available behavioral alternatives (15). A more appropriate measure of patients' attitudes toward hospitalization should assess attraction to the hospital as an alternative place to live in contrast to whatever living situation is realistically available to that patient in the community. Such a measure would constitute a patient's "living preference."

In an earlier study of hospitalized functionally psychotic patients considered suitable for discharge (16), we found that living preference, defined this way, could be assessed reliably by interviewing patients or staff and that living preference strongly predicted in-hospital days over a 9-month follow-up period. It was unclear whether long hospital tenure was due to failure to leave the hospital or recidivism. There is evidence that readmission and length of stay are separable aspects of hospital tenure and are associated with different risk factors (17, 18). It was also unclear whether living preference could be clearly observed from outside the hospital and would be a useful variable clinically.

The purpose of this study was to examine living preference in a community sample of chronically men-

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tally ill patients discharged from a state hospital. We addressed five specific hypotheses:

1. Living preference can be reliably assessed among chronically mentally ill outpatients.
2. Living preference can predict rehospitalization during a 1-year follow-up period.
3. For those patients who are rehospitalized, living preference can predict number of in-hospital days during a 1-year follow-up period.
4. The relationships between a) living preference and rehospitalization and b) living preference and number of in-hospital days are independent of psychiatric diagnoses.
5. These relationships remain significant when past hospitalization history is taken into account.

We will also discuss the clinical utility of focusing on living preference rather than on traditional correlates of hospital tenure.

METHOD

The subjects for this study were outpatients followed by Ambulatory Community Services, an aftercare service of the Cambridge-Somerville Mental Health and Retardation Center in Massachusetts. Established in 1973 to help state hospital patients in their reintegration into the community, Ambulatory Community Services is a mobile community-based team of mental health workers, nurses, and psychiatrists that provides and coordinates comprehensive community services for the most severely disturbed patients discharged from Metropolitan State Hospital to the Cambridge-Somerville area (19). Patients who need community services are referred while in the hospital and are followed in the community and during subsequent hospitalizations until they leave the catchment area. The caseload is biased toward patients with severe, chronic illness, since less disturbed patients do not get admitted to the state hospital or are not referred for comprehensive community services.

Each patient on the Ambulatory Community Services caseload during November and December of 1983 (N=259) was evaluated providing he or she 1) lived in the community, 2) was known by a caseworker well enough for attitude toward hospitalization to be evaluated (description of technique discussed later), and 3) had a primary *DSM-III* diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or personality disorder. The diagnosis was made according to hospital records and case review by one of the two Ambulatory Community Services psychiatrists. Wherever a disagreement between the records and case review occurred, the psychiatrist's judgment was used. These criteria eliminated 21 patients who were hospitalized at the time of evaluation, 32 patients who were not known well (14 because the mental health worker was just beginning and 18 because the patient was new or unwilling to be in treatment), and 10 patients who had primary diagnoses of alcoholism, dementia, or mental retardation. Nine additional patients were lost to follow-up (five died and four moved and could not be located).

The remaining sample of 187 patients had a mean±SD age of 40.1±12.1 years. All were between 20 and 65 because adolescents and the elderly were cared for in separate treatment facilities. The sample was 54.5% male and 45.5% female. Only 9% of the sample were married; 63% were single, and 28% were separated, divorced, or widowed. Only 11% were competitively employed. Past hospitalization history was measured as total time spent in any mental hospital and was rounded to the nearest half year; it ranged from a few months to 30 years (mean±SD=4.5±5.1 years). The distribution of the patients' primary *DSM-III* diagnoses was as follows: schizophrenia, 61% (N=115); schizoaffective disorder, 10% (N=18); bipolar disorder, 20% (N=37); and personality disorder, 9% (N=17).

As part of the initial assessment, 15 clinicians (11 mental health workers, three nurses, and one psychiatrist) were interviewed by a research psychiatrist (R.E.D.) about their patients' living preferences. Each of the mental health workers and nurses followed an independent caseload, while the psychiatrist rated the patients in a medication group (distributed across the 14 caseloads) as a check on interrater reliability. In addition, one case manager was reinterviewed 6 months after the initial assessment to evaluate the reliability over time, or stability, of living preference.

Before asking the clinicians to rate the patients' living preferences, the interviewer explained the concept of living preference: attitude toward the hospital as a place to live compared to current housing in the community. The clinicians were asked to classify each patient's living preference according to where the patient seemed to enjoy living and feel most comfortable, not according to staff's perception of the patient's severity of illness or need of hospitalization for treatment. The patients were assigned to three categories: 1) "prefers hospital"—the patient prefers living in the hospital, 2) "undecided"—the patient experiences some attraction to both living settings and is undecided about preference, or 3) "prefers community"—the patient prefers living in the current community living alternative.

Compared with patients' self-reports, ratings of living preference by case managers are, we believe, less influenced by current clinical state and by patients' well-documented tendency to comply superficially with staff's attempts to keep them out of the hospital (7). In our previous study (16), analogous ratings by hospital technicians agreed with ratings based on patients' answers to interview questions for 76% of the patients. Both sets of ratings predicted hospital tenure in that study, but the technicians' ratings did so more strongly.

After baseline data were collected from records and the ratings of living preference were made, the patients were followed prospectively for 12 months (the calendar year 1984). Hospital tenure was assessed in two dimensions: 1) *rehospitalization,* assessed as a dichotomous variable, and 2) for those patients who were rehospitalized, *in-hospital days,* or total number of days in a mental hospital during 1984. Number of in-hospital days during a set follow-up period is highly correlated with length of stay (20) but provides a more precise measure of the proportion of time spent in the hospital. In-hospital days probably represents a more meaningful outcome measure than rehospitalization, which can be brief, part of the treatment plan, and actually a positive event (3). Follow-up was performed by a research assistant who examined Ambulatory Community Services records, interviewed case managers to identify all hospitalizations, and checked the discharge summaries and hospital records from all hospitals to verify lengths of hospitalization.

TABLE 1. Relationship of Diagnosis, Rehospitalization Within 1 Year, and Patient Preference for Living in the Hospital or Community

Diagnosis and Living Preference[a]	Total Sample		Rehospitalized		Not Rehospitalized	
	N	%	N	%	N	%
All diagnoses[b]	187	100	80	43	107	57
Hospital attraction	44	24	30	68	14	32
Community attraction	143	76	50	35	93	65
Schizophrenia[c]	115	100	47	41	68	59
Hospital attraction	27	23	19	70	8	30
Community attraction	88	77	28	32	60	68
Schizoaffective disorder	18	100	9	50	9	50
Hospital attraction	6	33	4	67	2	33
Community attraction	12	67	5	42	7	58
Bipolar disorder[d]	37	100	18	49	19	51
Hospital attraction	5	14	5	100	0	0
Community attraction	32	86	13	41	19	59
Personality disorder	17	100	6	35	11	65
Hospital attraction	6	35	2	33	4	67
Community attraction	11	65	4	36	7	64

[a] Living preference was assessed by clinicians and defined as the patient's attitude toward the hospital as a place to live compared with current housing in the community. The "hospital attraction" group included both the patients who were felt to prefer the hospital and those considered undecided.

[b] $\chi^2=13.8$, df=1, p=0.0001.

[c] $\chi^2=11.2$, df=1, p<0.001.

[d] $\chi^2=4.0$, df=1, p<0.01 (expected frequency in two cells was less than five).

RESULTS

The mental health workers and nurses rated the patients' living preferences as follows: prefers hospital, N=12; undecided, N=32; prefers community, N=143. Because so few patients residing in the community were seen as having a definite preference for living in the hospital, we collapsed the "prefers hospital" and "undecided" groups into a single category of patients who experienced some attraction to the hospital and were called the "hospital attraction" group (N=44, 24%). These patients were then compared with the patients who experienced no attraction to hospital living and were called the "community attraction" group (N=143, 76%). To measure interrater reliability, an Ambulatory Community Services psychiatrist rated living preference for 46 patients. The raters agreed on 41 (89%) of the 46 cases, yielding a kappa (chance-corrected agreement) of 0.76 (21). Of these 41 agreements, 13 patients (32%) were attracted to the hospital and 28 patients (68%) were attracted to the community. To evaluate reliability over time, or stability, one case manager was reinterviewed 6 months after the initial assessment. The ratings agreed in 24 (86%) of 28 cases, yielding a kappa of 0.70. Eight (33%) of these 24 patients were attracted to the hospital and 16 (67%) to the community.

Of the 187 patients, 80 (43%) were rehospitalized at least once during the 1-year follow-up. A breakdown of rehospitalization rates by diagnosis is shown in table 1; the range was 35%–50%. These differences were not significant ($\chi^2=0.5$, df=3, p=0.33), indicating comparable proportions rehospitalized across diagnostic groups. On the other hand, living preference was a strong predictor of rehospitalization for the full sample and for the schizophrenic patients. As table 1 shows, hospital attraction was associated with rehospitalization in each case. The differences were in the expected direction for the patients with schizoaffective disorder and those with bipolar disorder, but the numbers were so small that the differences were not significant for the schizoaffective group and were of questionable validity for the bipolar patients. Living preference was clearly unrelated to rehospitalization for the patients with personality disorders.

The 80 patients who were rehospitalized had a mean±SD of 105.2±103.0 in-hospital days. The distribution was nearly symmetrical, forming a U-shaped pattern that reflected several cases at each end of the spectrum and explained the large variance. The number of in-hospital days was unrelated to diagnosis (one-way analysis of variance: F=1.33, df=3, 76, p=0.27). On the other hand, as table 2 illustrates, living preference strongly predicted time spent in the hospital. The associations between living preference and in-hospital days were in the expected direction (and of approximately similar magnitude) for the full sample and for each separate diagnostic category but were statistically significant only when the sample numbers were sufficiently large. Finally, living preference was unrelated to diagnosis ($\chi^2=4.3$, df=3, p=0.48), as table 1 shows.

Past hospitalization history, measured as number of years (to the nearest half year) of total previous hospitalization, was associated with living preference ratings (point biserial correlation=0.32, N=187, p<.01) but did not correlate significantly with either rehospitalization (point biserial correlation=.02, N=187, p=0.38) or number of in-hospital days (r=0.12, N=80, p=0.15). Furthermore, controlling for past hospitalization history did not affect the strength of the relationships between living preference and our two

TABLE 2. Relationship of Diagnosis, In-Hospital Days During 1-Year Follow-Up, and Patient Preference for Living in the Hospital or Community

Diagnosis and Living Preference[a]	N	Number of In-Hospital Days	
		Mean	SD
All diagnoses[b]			
Hospital attraction	30	156.6	125.3
Community attraction	50	74.3	89.9
Schizophrenia[c]			
Hospital attraction	19	175.2	140.5
Community attraction	28	89.9	112.0
Schizoaffective disorder			
Hospital attraction	4	107.5	71.1
Community attraction	5	65.6	44.5
Bipolar disorder[d]			
Hospital attraction	5	126.6	99.4
Community attraction	13	42.8	41.3
Personality disorder			
Hospital attraction	2	153.0	157.0
Community attraction	4	78.0	54.1

[a] Living preference was assessed by clinicians and defined as the patient's attitude toward the hospital as a place to live compared with current housing in the community. The "hospital attraction" group included both the patients who were felt to prefer the hospital and those considered undecided.

[b] $t=3.14$, $df=47$, $p=0.001$ (one-tailed test, separate variance estimates, degrees of freedom rounded to nearest integer).

[c] $t=2.31$, $df=45$, $p=0.01$ (one-tailed test, pooled variance estimate).

[d] $t=1.83$, $df=5$, $p=0.07$ (one-tailed test, separate variance estimates, degrees of freedom rounded to nearest integer).

measures of hospital tenure (according to partial correlation). Similarly, adding past hospitalization history did not affect the prediction model for stepwise logistic regression (22).

DISCUSSION

Hypothesis 1 was confirmed. Viewing living preference as a dichotomous variable, the raters were able to differentiate easily those who were attracted to the hospital from those who were not. The living preference ratings were reliable across raters and over time. Although 24% of the patients were assigned to the "hospital attraction" category, few of them were seen as actually preferring the hospital. There are several possible explanations for the low percentage of patients in the "hospital attraction" category. Previous studies that have found a high rate of patients expressing favorable attitudes toward the hospital were examining inpatients and were not specific about the reasons for hospital attraction (23). Inpatients may be attracted to the hospital because of anxiety about leaving (24, 25). Their attitudes tend to become less positive after discharge (26). Although many patients are also positive about the hospital at the time of readmission (7, 27), these patients may be "undecided" about living preference and shift their view in the direction of preferring the hospital at the time of readmission. Using a staff rating of living preference focuses attention on a more stable trait than the patient's self-report, which may be influenced by current clinical state and the tendency to comply with staff's attitudes.

Hypotheses 2 and 3 were also supported. Living preference appears to be a strong predictor of both rehospitalization and amount of time spent in the hospital for chronically mentally ill patients in the community. This study extends our previous finding that, for hospitalized psychotic patients, living preference can be assessed reliably and predicts number of in-hospital days (16). Attraction to the hospital as a living setting is not an artifact of current hospitalization. Some patients in the community continue to be attracted to the hospital, and their attitudes appear to influence subsequent hospitalizations.

The relationships between living preference and hospital tenure were relatively independent of diagnosis (hypothesis 4). For neither rehospitalization nor in-hospital days did the diagnoses show clear relationships with hospital tenure, while on the other hand, the relationships between living preference and hospital tenure were strong overall and the trends within the diagnostic categories were generally in the same direction. Moreover, diagnosis was unrelated to living preference.

Relationships between living preference and hospital tenure do not seem to be affected by past hospitalization history (hypothesis 5). The weak relationships in our data between past hospitalization history and hospital tenure were somewhat surprising and at variance with those in other studies (4–6, 16). However, not all studies have found such a relationship (28). The discrepancy may be explained by a recency effect. That is, history of hospitalization over the previous 12 months (or some other recent period) is more likely to predict future hospital tenure than history of hospitalization over an individual's lifetime, since older patients, even those with extensive histories of hospitalization, tend toward stability in the community when discharged (29).

Living preference is related to past hospitalization history and probably also to other factors, such as severity of illness, social supports, and institutional policies, that are widely believed to influence hospital tenure (2). We suggest, however, that patients' attitudes toward hospitalization, understood as their comparative attraction to hospital versus community living, represent a uniquely important synthesis of these factors, a synthesis that is operationalized by the patient. Recognizing living preference as a moderator that synthesizes the bearing of more traditional factors on hospital tenure seems important for the following conceptual, heuristic, and practical clinical reasons.

1. Living preference is a uniquely sensitive way of understanding various influences on hospital tenure because living preference takes account of idiosyncratic selection and weighting of factors. For example, the same job might be a stress, a support, or an unimportant factor for different patients. Presence of a

spouse might also be a stress, a support, or unimportant. Living preference avoids the false objectivity of treating these factors separately and as if their meaning stays constant across patients rather than as they are viewed by the patient. Living preference also explains one way in which these factors affect hospital tenure, i.e., through the patients' acting in accordance with preferred behavioral alternatives. Patients seem cognitively and interpersonally able to translate preferences into living locations.

2. Living preference partially explains the lack of comparability among many studies of hospital tenure. Since living preference is conceptualized as a complex interaction of institutional, community, and individual factors, we would predict the variability of results from study to study that has been found (30). Those factors will vary more in their predictive power than living preference, into which they feed.

3. Viewing traditional risk factors through the patient's eyes avoids the danger of imposing the observer's bias onto a patient. This has been an overwhelming problem in previous participant-observational research, such as that by Goffman (31), and, we suspect, in a great deal of clinical work. The crux of the issue is that each patient views institutions and communities through the lens of his or her own idiosyncratic background, values, beliefs, and wishes. Considering traditional risk factors from the patient's vantage point takes these differences into account.

4. Viewing the hospital and the community from the patient's idiosyncratic perspective also facilitates discharge planning. A patient who strongly desires to live in the community is likely to participate in treatment aimed toward that goal. On the other hand, a patient who is attracted to the hospital as a living alternative often subverts discharge planning unless the reasons for that living preference are addressed in the process. For example, a patient who is attracted to the hospital because of an alcoholic parent at home will be more likely to cooperate in discharge planning if that parent's alcoholism is treated or if the patient has some clear plan to cope with the alcoholic behavior. Since patients often adhere superficially to the expressed values of the hospital and staff—i.e., that living in the hospital is bad and that patients should be eager to leave—attraction to living in the hospital may be missed. When this occurs, the patient may do just the opposite of what is prescribed by staff for a successful discharge. For example, a patient may threaten or attack someone rather than walk away from a tense situation, knowing that such behavior will result in rehospitalization.

5. Recognizing and addressing living preference promotes an empathic connection between patient and clinician. For most chronically mentally ill patients, feelings about hospitalization and living situation are crucial. A clinician must appreciate these feelings to begin to understand the patient's world of personal meanings and to develop a treatment plan. For example, one patient who had been hospitalized many times finally acknowledged that he enjoyed the hospital's quiet grounds and library full of art books, that he feared home because of his alcoholic father, and that he attacked women on the subway to get back into the hospital. A treatment plan, including family therapy, activities, and a mechanism for returning to the hospital without violence, flowed easily from this focus on living preference. Accurate empathy is a cornerstone of good treatment, and this is no less true for case management than for psychotherapy.

6. Finally, thinking in terms of living preference allows us to make sense of behavior that otherwise might be misperceived as psychotic or irrational. The patient just described, for example, was seen as unpredictably violent as a result of several apparently random attacks against young women on the subway. When he finally admitted that these attacks served to facilitate his return to the hospital, we were able to set up an alternative pathway to the hospital, and the so-called "psychotic" violence stopped. Similarly, other patients have acknowledged that they became threatening, violent, self-destructive, or more blatantly psychotic to gain readmission or to prevent discharge. Chronically psychotic patients are capable of manipulating the system (32, 33), and the use of such behavior may actually be more common under the current administrative pressures to keep patients out of the hospital and to shorten the length of hospital stays.

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Validity of Subtyping Psychotic Depression: Examination of Phenomenology and Demographic Characteristics

Naomi Breslau, Ph.D., and Herbert Y. Meltzer, M.D.

The authors examine the validity of subtyping psychotic depression by comparing 111 patients with schizoaffective, unipolar, and bipolar psychotic depression on demographic characteristics and symptoms at index episode. Diagnoses were made by using Research Diagnostic Criteria (RDC). The three groups were indistinguishable in sex, race, and age at onset. Schizoaffective patients had more "schizophrenic" symptoms but were not different in depressive delusions, other psychotic symptoms, or affective symptoms. However, bipolar patients scored significantly higher than nonbipolar patients on hypomania. There is little support in these data for the schizoaffective versus nonschizoaffective distinction. Further tests are needed, including tests of response to treatment and biological markers.

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Recent research in affective disorder has focused on the significance of psychotic symptoms in major depression (1–5). Some phenomenologic, neuroendocrine, follow-up, and family studies (1, 3–13) have suggested that psychotic or delusional depression might signify a distinct subtype with respect to clinically important issues such as prognosis and response to treatment. Other studies failed to support the validity of psychotic depression as a distinct class (2, 14).

Nosologically, psychotic depression does not constitute a single diagnostic category. According to the Research Diagnostic Criteria (RDC) (15), depressed patients who manifest certain types of psychotic symptoms (i.e., the archetypal symptoms of schizophrenia, or first-rank symptoms) are classified as having schizoaffective disorder, whereas those without such symptoms are classified as having psychotic major depression. Further, like all patients who are diagnosed as having major depression, those falling in the psychotic subtype are subclassified according to their psychiatric history as bipolar or unipolar. In contrast with major depression, schizoaffective disorder is not formally divided into bipolar and unipolar, although such a distinction may be as useful for this disorder as it is for classical bipolar and unipolar disorder.

On the basis of empirical evidence that casts doubt on the diagnostic significance of the "schizophrenic" or first-rank psychotic symptoms in affective disorder (16), *DSM-III*'s definition of psychotic major depression does not separate patients with schizophrenic symptoms from patients with other psychotic symptoms. Rather, *DSM-III* divides depressed patients according to the mood congruence of their delusions and hallucinations. Most patients assigned by RDC to the schizoaffective depressed class would fall into *DSM-III*'s category of major depression with mood-incongruent psychotic symptoms (17).

The validity of RDC's subtypes of psychotic depression and *DSM-III*'s distinction between mood-congruent and mood-incongruent psychotic symptoms has important research implications. Strategies for investigating the diagnostic validity of delusional depression would differ if the category were shown to be a single, homogeneous class instead of a heterogeneous set of distinct subtypes such as unipolar, bipolar, and schizoaffective. (If the former alternative proved to be true, then depressed patients with psychotic symptoms would be classified as a single group to be contrasted with depressed nonpsychotic patients.)

Coryell et al. (18) reported that among patients with unipolar depression mood congruence had little prognostic significance and that the associations of mood congruence with illness rates in relatives were not significant. Similar findings were reported by Winokur (2). Subsequently, Coryell et al. (19) reported that at 6-, 12-, 18-, and 24-month follow-ups, both symptoms and social functioning did not differ significantly between unipolar patients with mood-congruent psychotic features and unipolar patients with mood-incongruent psychotic features. However, significant associations with mood congruence were reported from that study for cross-sectional phenomenology (20). Specifically, patients with mood-congruent delusions and hallucinations reported significantly more severe depressive symptoms than patients with mood-incongruent features. In that analysis, the mood-

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incongruent group differed also from the mood-congruent group in the proportion of patients with bipolar disorder—one-third versus one-tenth, respectively (six of 18 and six of 58, $\chi^2=3.868$, df=1, $p<0.05$), a difference that may have confounded the findings.

The importance of the unipolar-bipolar distinction has been supported by studies of family history, symptoms, treatment response, course of disease, and some biological measures, such as platelet serotonin uptake (21–23). Little attention, however, has been paid to the unipolar-bipolar dimension in *psychotic* depression. Winokur (2) reported differences in hallucinations and motor symptoms, but the two diagnostic groups were not different in demographic characteristics, family history, other symptoms, and course.

In this report, we will compare subtypes of psychotic depression on key demographic characteristics and on psychiatric symptoms at index episode. Patients classified as having schizoaffective depressed, mainly affective, disorder were compared with patients with psychotic major depression, unipolar and bipolar subtypes. Patients diagnosed as having schizoaffective, mainly schizophrenic, disorder were excluded from this analysis.

METHOD

The patients studied had been admitted on a voluntary basis to the inpatient research unit of the Laboratory of Biological Psychiatry of the Illinois State Psychiatric Institute, Chicago. All patients gave written informed consent and were assessed at admission by a battery that included the Present State Examination, 8th edition (PSE) (24), a psychiatric and family history schedule, the Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C) (25), and the Hamilton Rating Scale for Depression (26). Consensus RDC diagnoses were made at discharge on the basis of all the available information in a conference attended by research psychiatrists, a social worker who obtained intake information, nurses, and the raters who administered the assessment instruments.

In this research project, an expanded and modified SADS-C was used. Thirty-four items were added to provide the comprehensiveness needed in this research, and the original single item on psychomotor retardation was split into two items (items 51 and 52). Twenty-two of the added items focus on a more detailed assessment of hallucinations and delusions than that offered by the original SADS-C. Definitions of the added items were adopted from the PSE, but the scaling followed the SADS-C format. Six items of the original SADS-C were dropped because they either did not occur frequently in the study population or were not important for the research goals: phobias, obsessions or compulsions, excessive somatic concern, subjective evaluation of overall impairment, depersonalization, and weight gain.

Additionally, certain items were modified. Item 10 on psychic anxiety was expanded to include rather than exclude panic attacks. In item 15, loss of interest or pleasure, the anchors for ratings were altered to reflect the degree of loss rather than the range of activities affected, since this dimension is more pertinent to the way in which patients report this symptom. Item 17, subjective anger, was expanded to include rather than exclude anger directed inward. In item 18, ratings 5 and 6, which originally referred to persecutory delusions (dealt with separately in our modified SADS-C) were altered—the 5 rating indicated extreme suspiciousness and the 6 rating was omitted. In item 33, severity of hallucinations, provision was made for rating hallucinations definitely present even though the subject is aware they are in his or her imagination (this state was found to occur often in our patient population). In item 49, severity of delusions, ratings of questionable delusions and partial delusions were omitted because they are rated in newly added items elsewhere. In item 54, hyperactivity was expanded to include hyperactivity in general rather than being restricted only to agitation. In item 56, catatonic behavior, an index of severity was added to the original present-absent item. Finally, in item 61, irritability was expanded to include rather than exclude accompanying manic symptoms.

We report here on symptom clusters constructed from the SADS-C. Fourteen multi-item scales were formed by summing items measuring clinically determined symptomatic domains. Additionally, individual items of interest were used separately. This analysis is on 111 patients, approximately equally divided across the three diagnostic groups of schizoaffective, unipolar, and bipolar psychotic depression. Although the RDC do not classify schizoaffective into unipolar or bipolar, an examination of the *DSM-III* diagnoses of the schizoaffective group revealed that only 15% (six of 37) were classified as bipolar. Patients were included in the analysis if their records contained SADS-C data collected within 7 days of admission.

Our comparison of the phenomenology of psychotic depression covered a wide range of symptom clusters as well as individual symptoms. To correct for the increased probability that any one of the multiple tests would be significant by chance alone, the alpha level for the individual tests was set at 0.001. However, because of the exploratory nature of the investigation, we report all results that are significant at a nominal alpha of 0.05, even if they are not significant at alpha <0.001.

RESULTS

There were 34 patients in the schizoaffective group, 38 in the bipolar group, and 39 in the unipolar group. These three psychotic depression groups were indistinguishable in the percentages of patients who were male (35%, 32%, and 36%) and white (62%, 61%, and

TABLE 1. Scores on the SADS-C Psychotic Symptom Scales of Patients With Schizoaffective, Bipolar, and Unipolar Psychotic Depression

	Schizoaffective (N=34)				Bipolar (N=38)				Unipolar (N=39)			
	Patients With Symptoms		Score		Patients With Symptoms		Score		Patients With Symptoms		Score	
SADS-C Symptoms	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD
Schizophrenic symptoms												
First-rank (6 items)[a]	17	50	1.22	1.83	3	8	0.13	0.57	3	8	0.1[illegible]	0.58
Delusions of reference (1 item)[b]	21	62	1.65	1.42	12	32	0.69	1.15	9	23	0.5[illegible]	1.05
Other psychotic symptoms												
Depressive delusions (3 items)	14	41	1.61	2.19	19	50	2.60	2.77	19	49	1.9[illegible]	2.82
Grandiose delusions (2 items)	6	18	0.48	1.09	6	16	0.72	1.73	4	10	0.4[illegible]	1.34
Persecutory delusions (1 item)	19	56	1.28	1.35	20	53	1.20	1.35	15	38	0.7[illegible]	1.22
Auditory hallucinations (1 item)[c]	21	62			7	18			11	28		
Visual hallucinations (1 item)[d]	8	24			4	11			12	31		
Other hallucinations (2 items)[e]	12	35	1.11	1.77	7	18	0.37	0.88	7	18	0.3[illegible]	1.02
Catatonic/bizarre behavior (2 items)	7	21	0.60	1.31	3	8	0.21	0.77	3	8	0.6[illegible]	1.42
Thought disorder (3 items)[f]	17	50	2.31	3.54	16	42	1.21	2.00	4	10	0.5[illegible]	1.62

[a] Significant difference in mean scores (F=8.75, df=2, 108, $p<0.001$) and percents ($\chi^2=22.60$, df=2, $p<0.001$).
[b] Significant difference in mean scores (F=7.12, df=2, 108, $p<0.001$) and percents ($\chi^2=9.60$, df=2, $p<0.05$).
[c] Only percents were compared because item is coded as a dichotomy; significant difference in percents ($\chi^2=15.13$, df=2, $p<0.001$).
[d] Only percents were compared because item is coded as a dichotomy; significant difference in percents ($\chi^2=6.85$, df=2, $p<0.05$).
[e] Significant difference in mean scores (F=3.85, df=2, 108, $p<0.05$).
[f] Significant difference in mean scores (F=4.51, df=2, 108, $p<0.05$) and percents ($\chi^2=12.09$, df=2, $p<0.05$).

69%). The mean±SD ages at admission of the three groups were 33.0±10.8, 32.9±10.9, and 37.1±13.2 years; the difference was nonsignificant. Their ages at disease onset were 24.8±9.7, 23.6±7.4, and 26.3±11.2 years (data were available only for a subset of 65 patients, equally divided among the three groups). The patients diagnosed as bipolar had significantly more mean±SD years of education (13.3±2.3) than the patients with a schizoaffective (11.3±2.8) or unipolar (11.6±3.2) diagnosis (F=5.53, df=2, 108, $p<0.005$).

A comparison of the three groups on psychotic symptoms appears in table 1. The mean scores on the symptom scales and the number of patients with any symptom in the areas covered appear in the table. Analyses of variance (ANOVAs) were used to test the significance of differences in the means, and chi-square was used to test the significance of differences in the proportions of patients with any symptom. In the first part of the table, we present the results on symptoms regarded as typically schizophrenic. ANOVAs revealed significant differences on all the measures; schizoaffective patients scored markedly higher than either unipolar or bipolar patients on first-rank symptoms and delusions of reference. Chi-square tests yielded consistent results.

The results for other psychotic symptoms also appear in table 1. Comparisons on other hallucinations, thought disorder, auditory hallucinations, and visual hallucinations did not reach significance at 0.001, a level set to correct for the higher probability that any of the multiple tests would be significant by chance alone, but did reveal a trend toward significance ($0.001<p<0.05$). Other differences across the three diagnostic groups were minor and not statistically significant. When individual types of depressive delusions (guilt, nihilistic, or somatic) were examined, no significant differences were found, although unipolar patients had the highest rates of delusions of guilt and nihilistic delusions (data not shown). Schizoaffective patients did not score higher on depressive delusions or on any type of delusion in that domain.

Because of the possibility that group differences in other hallucinations and thought disorder reflected the associated excess in first-rank symptoms in schizoaffective patients, we repeated the analysis for patients negative for first-rank symptoms. The analysis was performed on 69 patients for whom data were available on all six first-rank symptoms. Nineteen patients with no evidence of first-rank symptoms in the available information were not studied because complete information was not available. Fifteen schizoaffective patients who did not report first-rank symptoms were compared with 54 nonschizoaffective patients (unipolar and bipolar) who did not report first-rank symptoms on other hallucinations and thought disorder. Differences in group means were not significant (t=0.001, df=67 for other hallucinations; t=1.77, df=67 for thought disorder). Comparisons on auditory and visual hallucinations yielded similar findings.

In table 2, we present the comparisons on nonpsychotic symptoms. With the exception of hypomanic symptoms, on which bipolar patients scored significantly higher than unipolar or schizoaffective patients, differences across the groups were not significant.

We also examined whether schizoaffective patients scored significantly lower than nonschizoaffective patients on the individual nonpsychotic depressive symptoms, as was reported by Coryell et al. (20) for patients classified according to the mood congruence of their psychotic features. The results appear in table 3. Differences across the three groups were not significant on any depressive symptom. Schizoaffective patients

TABLE 2. Scores on the SADS-C Nonpsychotic Symptom Scales of Patients With Schizoaffective, Bipolar, and Unipolar Psychotic Depression

SADS-C Symptoms	Schizoaffective (N=34)		Bipolar (N=38)		Unipolar (N=39)		F (df=2, 108)
	Mean	SD	Mean	SD	Mean	SD	
Depressive symptoms (13 items)	27.09	10.07	26.63	15.15	30.24	14.60	0.72
Hypomanic symptoms (10 items)	1.23	2.69	3.89	6.02	0.62	1.35	6.88[a]
Psychomotor retardation (2 items)	2.27	2.57	2.35	2.88	3.11	2.97	0.98
Agitation (3 items)	0.58	1.25	0.82	1.62	0.65	1.25	0.28
Anxiety (3 items)	7.25	3.07	7.50	2.93	7.39	3.90	0.05
Irritability/suspiciousness (3 items)	4.72	3.31	4.36	3.62	4.06	2.91	0.33
Blunted affect (2 items)	1.78	1.90	0.97	1.60	1.03	1.36	2.81
Lack of insight (1 item)	0.94	0.80	0.79	0.73	0.86	0.81	0.32

[a] $p<0.003$.

TABLE 3. Scores on the SADS-C Depressive Symptom Scales of Patients With Schizoaffective, Bipolar, and Unipolar Psychotic Depression

SADS-C Symptoms	Schizoaffective (N=34)		Bipolar (N=38)		Unipolar (N=39)	
	Mean	SD	Mean	SD	Mean	SD
Depressed mood/feeling	3.14	0.85	3.06	1.78	3.63	1.75
Diurnal mood variation	0.66	1.14	0.45	1.00	0.55	1.05
Reactivity/responsivity	1.25	0.70	1.00	0.79	0.93	0.83
Self-reproach	1.91	1.78	2.36	1.58	2.03	1.86
Negative evaluation	2.36	1.60	2.47	1.66	2.67	1.80
Discouragement	2.31	1.60	2.50	1.80	2.97	1.79
Suicidal ideation/acts	1.81	1.49	1.82	2.08	1.63	2.03
Insomnia	2.39	1.74	2.48	1.73	2.81	1.55
Fatigue	2.22	1.59	2.42	1.61	2.55	1.59
Appetite loss	1.55	1.62	1.49	1.91	1.53	1.59
Loss of sex interest	1.70	2.05	1.97	2.19	2.63	2.19
Depressed appearance	2.16	1.12	1.89	1.45	2.50	1.29
Weight loss	0.52	1.23	0.45	1.20	0.91	1.61

scored lower than nonschizoaffective patients on six of the 13 depressive symptoms but held an intermediate or highest rank on the remaining seven symptoms. A comparison of scores on the Hamilton depression scale at admission revealed no significant differences across the three groups. Bipolar patients scored the lowest, with a mean±SD of 26.37±10.99, compared with 28.44±9.63 and 29.00±11.93 for the schizoaffective and unipolar groups, respectively ($F=0.60$, $df=2, 108$, n.s.). Bipolar patients had lower ratings than unipolar patients on 10 of 13 depression items in table 3.

Two SADS-C items that measure severity of psychotic symptoms were also analyzed. The three groups differed significantly on severity of hallucinations ($F=7.47$, $df=2, 66$, $p<0.001$); schizoaffective patients scored higher than nonschizoaffective patients. Differences on severity of delusions were not significant. A comparison of schizoaffective versus nonschizoaffective patients on severity of hallucinations was repeated in patients negative for first-rank symptoms. The mean rating of the 15 schizoaffective patients with no first-rank symptoms for whom data were available was only slightly and not significantly higher than that of the 54 nonschizophrenic patients with no first-rank symptoms for whom data were available ($t=1.15$, $df=67$).

DISCUSSION

The key findings of this analysis can be summarized as follows.

1. Patients with psychotic depression diagnosed according to RDC as schizoaffective, bipolar, or unipolar were indistinguishable in sex, race, and age at onset. Patients with bipolar disorder had, on the average, a significantly higher level of education.
2. A comparison of psychotic symptoms at index episode revealed significant differences on the set of symptoms specified by RDC as the "schizophrenic" criteria in schizoaffective disorder. Differences on other psychotic symptoms were not significant.
3. The hallucinations of patients with schizoaffective disorder were rated as significantly more severe than those of patients with unipolar or bipolar psychotic depression, a difference that appears to be explained by the influence of the presence or absence of first-rank symptoms on the severity assessment of all hallucinations. When schizoaffective patients negative for first-rank symptoms were compared with nonschizoaffective patients who were also negative for first-rank symptoms, differences were slight and not significant.
4. On the nonpsychotic symptom scales, differences were not significant, with one exception—the hypomania scale.
5. On the hypomania scale, bipolar patients scored significantly higher than unipolar and schizoaffective patients, indicating a mixed clinical picture, with manic and depressive symptoms present concurrently.
6. On depressive symptoms, the three groups showed similar configurations; differences were slight and nonsignificant.

There is little support in these results for the validity of separating psychotically depressed patients into those with schizoaffective or nonschizoaffective psychotic depression. Aside from the more frequent presence of those psychotic symptoms which formally define the schizoaffective category, no symptomatic features characterized schizoaffective patients as a distinct category. Moreover, schizoaffective patients were similar to unipolar and bipolar psychotic patients in sex and race as well as age at onset. The similarity of the male-to-female ratios in the three groups is particularly instructive. In conforming to the male-to-female sex ratio in affective disorder (i.e., 1:2), the sex ratio of patients with schizoaffective disorder sharply departs from the pattern observed in the prevalence rates of treated schizophrenia—approximately 1:1 (27). Note that in the clinical setting of this study, schizophrenic patients also showed a 2:1 predominance of men.

We did not find in these data any evidence that patients with mood-incongruent features, operationalized as meeting criteria for schizoaffective disorder, exhibited a less severe depressive syndrome, a finding reported by Coryell et al. (20). The negative results on the value of the RDC schizoaffective criteria for defining a distinct phenomenologic subtype of psychotic depression are in accord with previous findings on treatment outcome, long-term course, and family aggregation (2, 16, 19). None of these studies, however, compared the phenomenology at index episode in schizoaffective versus nonschizoaffective psychotic major depression. The disparity between our results and those of Coryell et al. (20) might in part be accounted for by differences between the two studies in the diagnostic assignment of patients with a history of mania. In our sample, only a few (10%) of the psychotically depressed patients with a history of mania were classified as schizoaffective, constituting 15% of the schizoaffective subset; the remaining 90% of the patients fell into the nonschizoaffective category and constituted the bipolar group in this analysis. In contrast, in the Coryell study, one-half of the psychotically depressed patients with a history of mania were assigned to the mood-incongruent class, in which they constituted a full third of the total. Although we did not find that bipolar patients scored significantly lower than nonbipolar patients on depressive symptoms, they did score lower on depressed appearance, depressed mood, and several other depressive symptoms as well as on the Hamilton depression scale. Comparisons between schizoaffective patients with a history of mania and schizoaffective patients negative for mania yielded a similar trend. Clearly, an examination of the significance of mood-incongruent psychotic symptoms should control for the potential effects of polarity.

Our results underscore the diagnostic significance of affective polarity in other and more important ways. Bipolar patients, in contrast with nonbipolar patients, manifested mixed manic and depressed symptoms; additionally, they had higher levels of educational achievement. Although the significantly higher educational achievement among bipolar patients is ambiguous, reflecting either a social class advantage or a less functionally impaired history, the distinctive presence of manic symptoms constitutes evidence of diagnostic integrity that goes beyond definitional confirmation, since the classification of bipolar disorder in depressed patients is based on psychiatric history and is independent of the nature of symptoms that characterize the depressive episodes.

There is evidence in these data that the presence of first-rank symptoms in psychotic depression may incline raters to overstate the symptoms in other domains, specifically, hallucinations of other types (i.e., those not included in the first-rank class) and thought disorder, as well as the severity of all hallucinations. An alternative interpretation of these findings might be that first-rank psychotic symptoms are in fact accompanied by other hallucinations, loosening of associations, or other features of disordered thinking and generally more severe hallucinations of all types. An empirically based answer to this question would require other research approaches. We speculate, however, that the attribution of a unique diagnostic significance to certain types of hallucinations (Schneiderian) may have endowed them with added clinical weight, influencing observers' judgment of the severity and pervasiveness of all psychotic pathology.

The results of this study indicate that schizoaffective depression, mainly affective, is closely related to unipolar and bipolar psychotic depression and that the last two affective psychoses are essentially similar in depressive and psychotic symptoms, with the exception of hypomania, which is more common in bipolar patients. The extent to which hypomanic symptoms color the psychotic depressive episode of bipolar patients is an issue that requires further investigation. On balance, it would appear that on the basis of symptoms, all three types of affective psychoses may be considered a single, relatively homogeneous group. Further research is needed to determine how similar these groups are in treatment response and biological measures.

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Sex Differences in Recurrent Depression: Are There Any That Are Significant?

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The authors report on sex differences in a group of 230 patients with recurrent depression. Male and female patients were similar in clinical characteristics and baseline measures of severity. Some sex differences in depressive symptoms were apparent, especially as reflected by self-report instruments. The women reported more appetite and weight increase, more somatization, and expressed anger and hostility. The men demonstrated a more rapid response to treatment. Various interpretations of these findings are discussed.
(Am J Psychiatry 1988; 145:41–45)

A common clinical observation is that women constitute the majority of patients given a diagnosis of depression. Weissman and Klerman (1) carefully examined a variety of explanations for the preponderance of women in both clinical and nonclinical samples and concluded that the different rates are real: the higher prevalence of primary affective disorders among women is not an artifact of reporting or care-seeking behavior. Not only do fewer men experience depression, but depressed men are also less likely to seek treatment (2). Consequently, it has been difficult to amass large clinical samples of men with pure and homogeneous diagnoses.

Data on sex differences in depression have frequently been derived from nondepressed or mildly depressed subsamples of college students or community survey respondents (3, 4). While such research provides much useful information about the different depressive symptoms reported by men and women, it is not clear that these findings are generalizable to individuals who seek psychiatric treatment and meet diagnostic criteria for primary affective disorder. Since the existing literature on sex differences in large clinical samples is scarce, this study was designed to be exploratory in nature. We used a large number of both clinician-rated and self-report instruments describing clinical characteristics, depressive symptoms, and personality features, as well as information on the rate of response to combined treatment, of 230 recurrently depressed outpatients. Our goal was to uncover and understand any male-female differences that might emerge.

METHOD

The subjects for this investigation were 230 individuals (180 women and 50 men) recruited through self-referral, medical referral, and a broad-based public information campaign on depressive illness for a long-term study of maintenance therapies for recurrent depression. Subjects were required to be between the ages of 21 and 65 years and to be in at least their third episode of definite major depressive disorder according to the Research Diagnostic Criteria (RDC) (5), with the immediately preceding episode having occurred no more than 2½ years before the onset of the index episode. All patients had experienced at least a 10-week period of remission before their index episode. A Raskin severity of depression (6) score of 7 or more and a Hamilton Rating Scale for Depression (single rater, 17-item version) (7) score of 15 or more at each of two evaluations spaced 2 weeks apart were also required for admission to the protocol.

After initial evaluation, all patients received the same acute treatment regimen, which consisted of pharmacotherapy (imipramine, 150–300 mg/day) and interpersonal psychotherapy (8). Patients were seen weekly for the first 12 weeks, biweekly for the next 8 weeks, and then monthly until they had completed a continuation treatment period of 20 weeks during which their drug doses did not change and their rating scale scores remained stable and consistent with a clinical remission (Hamilton score ≤7, Raskin score ≤5).

The RDC protocol and the full Schedule for Affective Disorders and Schizophrenia (SADS) (9) were administered at the time of initial screening. The Hamilton depression scale, the Raskin depression scale, the Global Assessment Scale (GAS) (10), the Beck Depression Inventory (11), and the Hopkins Symptom Checklist (SCL-90) (12) were given before

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the drug-free washout period and again before treatment. Our revised Hamilton scale was an expanded version of the standard 17-item scale; it included additional items assessing increased appetite, weight gain, diurnal variation in mood, three separate dimensions of hypersomnia, and two types of retardation (psychic and motoric). The additional eight items were scored in the standard 0–2 or 0–4 fashion.

At the end of 16 weeks of acute treatment, patients were classified as normal responders, slow responders, or partial responders/nonresponders. Response type was determined by using a computer algorithm that took into account the patient's Hamilton score after 8, 12, and 16 weeks of treatment. Normal responders were characterized by a rapid and sustained recovery completed in 8 weeks, while slow responders either took longer to become asymptomatic or showed a more varied course of recovery. Partial responders/nonresponders completed the 16 weeks but failed to meet the criteria for recovery. Fourteen percent (N=25) of the women and 10% (N=5) of the men terminated treatment before 16 weeks for reasons including noncompliance with the treatment regimen, inconvenience to the patient, and side effects of the medication.

Personality was assessed at the end of the continuation treatment, at which time both the Hamilton and Raskin scores and the imipramine dose were required to have been stable for 17 weeks. The assessment was made according to a personality battery described by Hirschfeld et al. (13, 14)—a 436-item self-report inventory composed of 17 scales drawn from five preexisting personality inventories—and the Personality Assessment Form (15), a structured interview designed to assess personality on the basis of the *DSM-III* personality disorder categories. The personality battery was constructed for use in the National Institute of Mental Health (NIMH)-Clinical Research Branch Collaborative Program on the Psychobiology of Depression. The Personality Assessment Form interview was developed for use in the NIMH Treatment of Depression Collaborative Research Program and was further refined for use in the present protocol. The Personality Assessment Form was administered, also at the end of the continuation treatment, by the subject's primary clinician (a psychiatric social worker or a clinical psychologist), who asked a series of 15–25 standardized probe questions for each *DSM-III* category and then rated the extent to which the subject conformed to the description of each of the *DSM-III* personality disorders.

Variables describing clinical characteristics and baseline assessments were analyzed with two-tailed t tests. When differences in depressive symptoms between the male and female groups were examined, a score of 3 or more on a SADS item was considered to indicate that a symptom was present and a score of 1 or 2 that a symptom was absent. With the symptoms categorized in this way, chi-square tests were performed on 23 SADS items characteristic of dysphoric affective disturbance. In order to take the multiplicity of comparisons into account, the Bonferroni inequality correction was applied, so that an individual SADS item required an alpha of 0.004 for it to be significant.

Ten standard SCL-90 factor scores (12) were analyzed with t tests at baseline, 8 weeks into the acute phase, and at 16 weeks. All available data from the patients who were still active in the protocol at each time point were used in the analyses. In this instance the Bonferroni correction yielded an alpha of 0.01 for rejecting the null hypothesis.

Sex differences in scores on the personality battery were tested with a multivariate analysis of variance (MANOVA) composed of all 17 personality constructs and one factor (sex). The Personality Assessment Form diagnostic categories were individually examined with chi-square tests; scores of 1–3 were considered to indicate that a personality disorder was absent, and 4–6 indicated that one was present. The alpha for each individual diagnostic category was set at 0.008, so as to achieve an overall alpha of 0.10.

RESULTS

As table 1 indicates, the women and the men were similar with respect to age at screening, age at onset of depression, number of previous episodes, and duration of the index episode. There were no differences between the mean scores of the two groups on any of the clinician-rated baseline assessments of overall severity (17-item Hamilton depression scale, Raskin depression scale, and GAS). However, women showed a significantly higher total score on both self-report scales, the Beck Depression Inventory and the SCL-90. In addition, the revised Hamilton depression scale yielded a significantly higher score for women than for men, although no significant sex differences were apparent on the traditional 17-item Hamilton scale.

Comparison of the numbers of women and men who fell into the definite, probable, and absent categories of RDC depression subtype diagnoses revealed no significant differences between the two groups on any of the subtypes we examined (bipolar II, incapacitating, endogenous, agitated, and retarded).

Table 2 shows the percentages of each of the sexes who reported on the SADS that they experienced depressive symptoms to at least a moderate degree. The women were more likely to report increased appetite and weight gain and less likely to report weight loss than their male counterparts. More women than men reported experiencing somatic anxiety, expressed anger, and hypochondriasis; however, when the conservative alpha level required by the Bonferroni correction was used, only expressed anger significantly differentiated the women from the men.

Of the 10 SCL-90 factors (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ide-

TABLE 1. Clinical Characteristics and Baseline Assessments of Female and Male Patients With Recurrent Depression

	Women (N=180)			Men (N=50)		
Item	Mean	SD	Median	Mean	SD	Median
Clinical characteristics						
Age (years)						
At screening	39.3	10.5	38.0	40.2	11.0	38.0
At onset of first episode	26.0	11.2	25.0	27.3	12.2	24.0
Number of previous episodes	6.2	5.6	4.0	6.4	7.3	4.0
Duration of index episode (weeks)	22.1	17.4	16.0	24.6	18.2	23.0
Baseline assessments						
Hamilton 17-item depression score	22.2	4.4	22.0	21.8	5.1	21.5
Revised Hamilton depression score[a]	27.3	5.3	26.0	24.8	7.5	26.0
Raskin depression score	10.4	1.7	10.5	10.2	1.9	10.0
GAS score	49.5	8.6	51.0	49.3	8.4	51.0
Beck inventory score[b]	28.6	7.6	28.0	24.5	8.4	22.5
SCL-90 score[c]	2.3	0.5	2.3	2.0	0.6	2.0

[a] Significant difference in mean value between groups ($t=2.06$, $df=58$, $p<0.05$, two-tailed test).
[b] Significant difference in mean value between groups ($t=-2.82$, $df=164$, $p<0.005$, two-tailed test).
[c] Significant difference in mean value between groups ($t=-3.56$, $df=181$, $p<0.001$, two-tailed test).

TABLE 2. SADS Symptoms Reported at Baseline by 179 Female and 49 Male Patients With Recurrent Depression

SADS Item Number	Symptom	Women[a]		Men[a]	
		N	%	N	%
320	Increased appetite	81	49	13	28
317	Decreased appetite	95	53	34	68
321	Weight gain	71	43	12	26
319	Weight loss	46	28	21	45
314	Hypersomnia	61	37	17	36
272	Insomnia	155	87	43	88
334	Psychomotor agitation	71	40	15	30
342	Psychomotor retardation	73	41	18	36
315	Anergia	172	88	43	82
351	Diurnal morning variation in mood	79	45	21	42
352	Diurnal evening variation in mood	47	27	7	13
263	Somatic anxiety	151	84	34	69
265	Psychic anxiety	150	84	41	84
246	Suicidal tendencies	114	64	36	72
267	Phobia	31	17	5	10
270	Obsessive-compulsive symptoms	9	5	2	4
322	Hypochondriasis	42	24	4	8
350	Reactivity	152	93	44	96
325	Slowed thinking	156	95	45	96
328	Social withdrawal	154	94	40	85
329	Derealization	23	14	5	11
330	Anger (subjective)	157	88	41	82
332	Expressed anger[b]	125	70	24	48

[a] For each symptom, percentages are based on the number of subjects for whom data were available.
[b] Significant difference between groups ($\chi^2=8.5$, $df=1$, $p<0.004$). The Bonferroni inequality correction applied to the overall alpha of 0.10 yielded an individual item alpha of 0.004.

ation, psychoticism, and additional scales), scores on five showed significant sex differences at one or more of the three assessment times (baseline, 8 weeks, and 16 weeks) (see table 3). In each instance, the mean score for the women was higher than the mean score for the men. There was a trend for the women to describe more somatization than the men at baseline and at 8 weeks; this difference became even more pronounced by the end of the acute treatment period. The obsessive-compulsive score was higher for the women than for the men at 16 weeks, but before that point it showed no significant sex difference. Depression factor scores for women tended to be higher than for men at the initiation of treatment, and by the halfway point this difference had become more marked. However, by the end of the 16 weeks, significant sex differences on the depression factor had disappeared. The women's anger-hostility score was significantly higher than that of the men at baseline only; the two groups were similar at subsequent assessments. Finally, the 10th factor, additional scales, appeared to tap a variety of depressive symptoms that not only discriminated between the sexes at baseline but also resulted in increasingly different mean scores as both groups progressed toward recovery from the acute episode.

A MANOVA performed on the personality battery data showed a significant overall sex difference (Hotelling's $t^2=59.53$, $df=7, 105$, $p=0.0003$). Women scored significantly higher on the ego control scale ($t=2.67$, $df=122$, $p=0.009$), while men scored higher on the assertion of autonomy scale ($t=-2.45$, $df=122$, $p=0.016$). The only notable sex difference seen on the Personality Assessment Form occurred in the compulsive personality category. Significantly more men (41%, N=11) than women (11%, N=9) met the criteria for this diagnosis ($\chi^2=9.49$, $df=1$, $p=0.002$).

Once treatment terminators were eliminated from the sample, there was no difference between the sexes in the likelihood of achieving recovery by the end of 16 weeks; however, men were more likely to be categorized as normal responders. Forty-nine percent (N=22) of the male completers and 32% (N=49) of the female completers showed a normal response by our criteria ($\chi^2=4.80$, $df=1$, $p=0.029$). There was no significant sex difference in the number of treatment terminators from each group.

TABLE 3. Significant Differences in Mean SCL-90 Factor Scores of Female and Male Patients With Recurrent Depression

	Significance of Difference in Mean Score Between Men and Women[a]		
SCL-90 Factor	Baseline (175 women and 48 men)	8 Weeks (151 women and 43 men)	16 Weeks (144 women and 43 men)
Somatization	$t=1.87$, df=217, $p<0.10$	$t=2.24$, df=90, $p<0.05$	$t=2.19$, df=178, $p<0.05$
Obsessive-compulsive	n.s.	n.s.	$t=2.17$, df=117, $p<0.05$
Depression	$t=1.86$, df=210, $p<0.10$	$t=2.07$, df=100, $p<0.05$	n.s.
Anger-hostility	$t=2.47$, df=216, $p<0.005$	n.s.	n.s.
Additional scales[b]	$t=2.09$, df=216, $p<0.05$	$t=2.95$, df=95, $p<0.005$	$t=3.27$, df=128, $p<0.002$

[a] In all cases where a p value is reported, the mean factor score for women was higher than the mean factor score for men. Data from all patients still active in the protocol at each time point were analyzed, hence the numbers diminish slightly over time.

[b] This factor includes items assessing poor appetite, overeating, various sleep disturbances, thoughts of death, and feelings of guilt.

DISCUSSION

This investigation was aimed at exploring possible sex differences in the expression of recurrent depression. In general, we found that the men and the women were similar in clinical characteristics and baseline measures of severity. However, some sex differences in depressive symptoms were apparent, especially as reflected by self-report instruments.

One approach to interpreting the results of the study is to accept these findings as indicators of real sex differences in the phenomenology of the disorder. The clinician-rated SADS items that approached significance (appetite and weight increase, hypochondriasis, somatic anxiety, and expressed anger) were often the same as the items significantly more frequently endorsed by women on self-reports. Furthermore, the addition of several new items to the Hamilton depression scale (hypersomnia, weight and appetite increase, diurnal variation, and retardation) resulted in significant baseline differences that did not exist with the original 17-item version. Post hoc analyses of those additional Hamilton items showed that women reported more weight gain at baseline. Taking all modes of assessment into consideration, it appears highly likely that increase in appetite and weight gain are features of depression more common to women than to men.

Expressions of anger and hostility were clearly more characteristic of women than of men at baseline. However, this difference disappeared, even in the self-report data, by the 8-week point in treatment. One could hypothesize that the interpersonal psychotherapy all patients received contributed to the resolution of interpersonal concerns which may have burdened the women in particular at the onset of their episodes.

One especially notable finding was a sex difference in the rate of response to our acute treatment regimen. The men wre significantly more likely to show a rapid and sustained clinical response than the women, as indicated by the percentages of each group classified as normal responders. This is particularly interesting in light of the lack of differences between the sexes when baseline clinical characteristics and level of severity of depression were examined. This finding might be attributable to sex differences in reporting and in symptom denial, but it could also be true that combined pharmacologic and psychotherapeutic treatment of affective illness is likely to bring about a more rapid favorable outcome in men than in women. If we hypothesized that the normal responders were responding primarily to the pharmacotherapy, while the slow responders needed both the pharmacotherapy and the slower-acting psychotherapy, it would be tempting to interpret this finding as an indicator that the depression of women is more interpersonally based than the depression suffered by men. However, the data from this study cannot provide empirical support for such a contention.

An alternative interpretation of these findings might hold that the differences we observed simply reflect socioculturally determined differences in the ways in which men and women perceive their problems and behave in response to them. Since the statistically significant sex differences were found almost exclusively on self-report inventories, it is possible that these differences reflect the greater willingness of women to acknowledge and express symptoms in such a format (16). Briscoe (17) concluded that women are more likely than men to identify both pleasant and unpleasant feelings and are more aware of symptoms. Warren (18) provided evidence that men inhibit expression of depression because it is incompatible with the male sex role and masculine socialization. Further analyses of our self-report data indicated that the baseline sex differences in severity scores persisted at the end of the 16-week treatment phase, by which time all patients had recovered. This lends additional support to one "artifact" explanation: that different degrees of ability to recognize symptoms or willingness to report them accounts for the observed differences in the depressive syndromes of men and women.

Taking another perspective on sex differences in reporting style, one might view men as engaging in more denial of symptoms than women. Some researchers found that the significant sex difference in help-seeking behavior occurred in the first stage of problem recognition (19). Once men acknowledged that they had an illness, they were found to be as likely as women to seek professional help. If this were the case, we might imagine that by the time our male subjects came to the clinic for treatment of their depression, their denial and defense mechanisms had been broken down, making them appear very similar clinically to the women. Perhaps once they began to recover, the men resumed their old habit of symptom denial and this was reflected in their significantly lower Hamilton score after 8 weeks, which in turn resulted in more men being categorized as rapid responders. Since sex differences in patient-reported symptoms became even more significant over time during the recovery phase, it is possible that the men were returning to their predepression style of symptom denial.

In conjunction with the sex differences in patient reporting that we have described, it is conceivable that there is a complementary difference in clinicians' thresholds for rating patients' symptoms as positive. Perhaps evaluators tend to discount some portion of the numerous symptoms reported to them by women and pay somewhat greater attention to, or give greater weight to, the few symptoms described by men. Such an explanation could account for the absence of significant sex differences in clinician-rated assessments.

The women described themselves, both at baseline and after 16 weeks of acute treatment, as suffering from significantly more somatic problems, which was reflected in the SCL-90 somatization score. We cannot determine, on the basis of these data alone, whether women actually experience more somatization in the manifestation of their affective illness or whether they are simply more concerned with and attuned to their bodily symptoms and changes. Clinicians described 24% of the women and only 8% of the men as hypochondriac on the SADS, suggesting that more women were preoccupied with their bodily functions and physical illness.

In sum, the highly selected group of male and female depressed patients we studied appeared to be remarkably similar in the manifestation of their illness. Clearly, more investigation is needed to determine whether biological factors can account for the sex differences that were noted in initial symptoms (weight and appetite increase, somatization, expressed anger, and hostility) and for the potentially most important sex difference, rate of treatment response.

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Influences of Time, Ethnicity, and Attachment on Depression in Southeast Asian Refugees

Morton Beiser, M.D.

The author reports on a study investigating the question of whether certain phases of resettlement are accompanied by an elevated risk for depression in Southeast Asian refugees in Canada. In general, the longer the Southeast Asian refugees remained in Canada, the better their mental health. However, unmarried or otherwise unattached Laotians and Vietnamese refugees experienced high levels of depression 10–12 months after arrival. Two years after the initial investigation, this group, disadvantaged by a lack of social resources, continued to be more depressed than other refugees.

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In a world with at least 10 million refugees (1), countries of asylum like Canada and the United States must consider how to provide for the specialized needs of displaced persons whom they admit as immigrants. Studies (2–13) have suggested that refugees experience more mental and physical disorders than the indigenous population and that they require specialized forms of treatment.

One of the most interesting suggestions arising from past studies is that the risk for developing mental disorders is not particularly high immediately after arrival in the country of resettlement. Instead, after an initial "incubation" period, mental disorders begin to emerge months later, ushering in a peak period of mental health risk (2–8). If valid, this concept of phase-related risk suggests when intervenient services might be introduced for maximum effect. However, this idea, which has become widely accepted, derives from a surprisingly small number of clinically based and, therefore, methodologically limited studies. A study by Rumbaut (8) that used a community sample of Southeast Asian refugees living in San Diego offers a significant advance; however, the cross-sectional data in this report suffer a potential confounding of time with cohort effects.

In this paper I examine a representative community sample of Southeast Asian refugees, using both cross-sectional and longitudinal data to ascertain whether a specific phase of elevated risk for mental disorder occurs during the early years of resettlement. In addition, I address some personal and social contingencies affecting adaptation to a new environment.

HISTORICAL BACKGROUND

The 1970s were witness to two large out-migrations from Southeast Asia. Most of the refugees in the first exodus, precipitated by the fall of Saigon in 1975, resettled in the United States. Vietnam's subsequent invasion of Kampuchea, which set in motion a war between Vietnam and China, initiated a new wave of refugeeism during which other countries, including Canada, joined the United States in becoming places of permanent asylum. In 1978 and 1979, the government of Vietnam began evacuating ethnic Chinese still residing in that country who could pay the exit fee (approximately one bar of gold per family member). Some Vietnamese families secured exits by claiming Chinese ancestry and paying the fee; others escaped the country through the more permeable but still dangerous borders. Following the North Vietnamese occupation of their country, large numbers of Laotians also became refugees.

Patterns of exodus varied among the ethnic groups. The Chinese and Laotians were more likely to emigrate as families, whereas among the Vietnamese, one person frequently departed alone with the idea of earning enough money to sponsor others at a future date.

Canada admitted 70,000 refugees between 1979 and 1981. Approximately 7,000 refugees resettled in Vancouver, British Columbia, and another 350 in rural areas outside Vancouver.

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METHOD

The University of British Columbia Refugee Resettlement Project is a study of refugees from Vietnam and Laos during their first four years of life in Canada. The project began in 1981 with a survey of 1,348 adults, a group made up of a one-in-three sample of all adult refugees who had settled in Vancouver plus all 350 Southeast Asian refugees who settled in the nearby rural areas. Beginning with name lists supplied by refugee agencies and key informants, we approached refugee households, enumerated all the adults living in them, and selected, by probability methods, a subject within the household for study. Sampling was stratified to produce equal numbers of Chinese and non-Chinese respondents. All subjects were informed of the nature of the study and provided written informed consent. Details of the procedure have been described more fully elsewhere (14). The overall completion rate was 97%. Twenty-four months after the initial survey, we again interviewed 1,169 persons, 87% of the original sample. Questions on health, mental health, health-care seeking, value orientation, social support, and experiences with the economic system in Canada were translated into Cantonese, Vietnamese, and Laotian, then translated back into English. A panel of bilingual consultants resolved any difficulties in the translations. This technique, successfully used in a number of cross-cultural studies, helps to overcome problems inherent in literal translations carried out by one person (15). The interview schedule was then administered to the refugees by bilingual individuals, most of them refugees, who had been trained in the technique of structured interviewing.

Depression, the subject of one of four scales constructed on the basis of a factor analysis of the mental health portion of our interview schedule, constitutes the focus of this report. Items making up this 17-question scale derive from a number of measures used in other epidemiological surveys (16–18). In addition, we included a number of culture-specific items derived from ethnographic investigations of the ways in which distress is expressed in Vietnamese and Laotian cultures. Our depression inventory, which contains questions such as "Have you been feeling sad?" and "Have you been feeling that you are a worthless person?" are all answered by "often," "sometimes," or "never" with reference to the past 4 weeks. (For a full description of the scale and its construction, see reference 14.) This measure, developed specifically for the current study, addresses the issue of cultural specificity in reporting symptoms but, in retaining a core of items widely used in Euro-American surveys, makes comparisons with other studies possible. The scale has excellent psychometric properties. Furthermore, the impressive factoral invariance in a North American sample compared with the sample of Southeast Asian refugees (14, 19) marks it as a useful cross-cultural measure.

In order to examine the relationship between depression and phase of resettlement, we divided the refugees into groups according to the length of time they had been in Canada when first interviewed for our study: 3 months or less, 4–6 months, 7–9 months, and so on.

Previous studies (20–22) suggest that social support mitigates the effects of stresses, such as those of resettlement, on mental health. Murphy (23) asserted that an immigrant's ethnic group in the country of resettlement becomes an important source of that support. Lin and Ensel (21) presented data illustrating that social support from persons with a shared ethnic background exerts a directly beneficial effect on mental health as well as a buffering effect following stressful events. Since Vancouver boasts one of the largest Chinese communities in North America, we predicted that Chinese refugees would be more advantaged than the relatively small groups of Vietnamese and Laotians. We also predicted that people fortunate enough to have arrived in intact family groups would experience better mental health during the early years of resettlement than people in other situations.

Analyses of the relationship between time of arrival in Canada and risk of depression included controls for ethnicity and family situation because there was reason to believe that these characteristics were not randomly distributed over the immigration study groups. Early in the resettlement program, families were given preference over single people; therefore, adult members of earlier immigrant groups might be more likely to have been married and entering Canada with their spouses, whereas later groups could have contained more never-married people or those forcibly separated from their spouses. The Chinese pattern of exodus from Vietnam differed from that of the Vietnamese. Since the former were more likely to leave in family groups, Chinese were heavily represented among the earlier and Vietnamese among the later groups of immigrants.

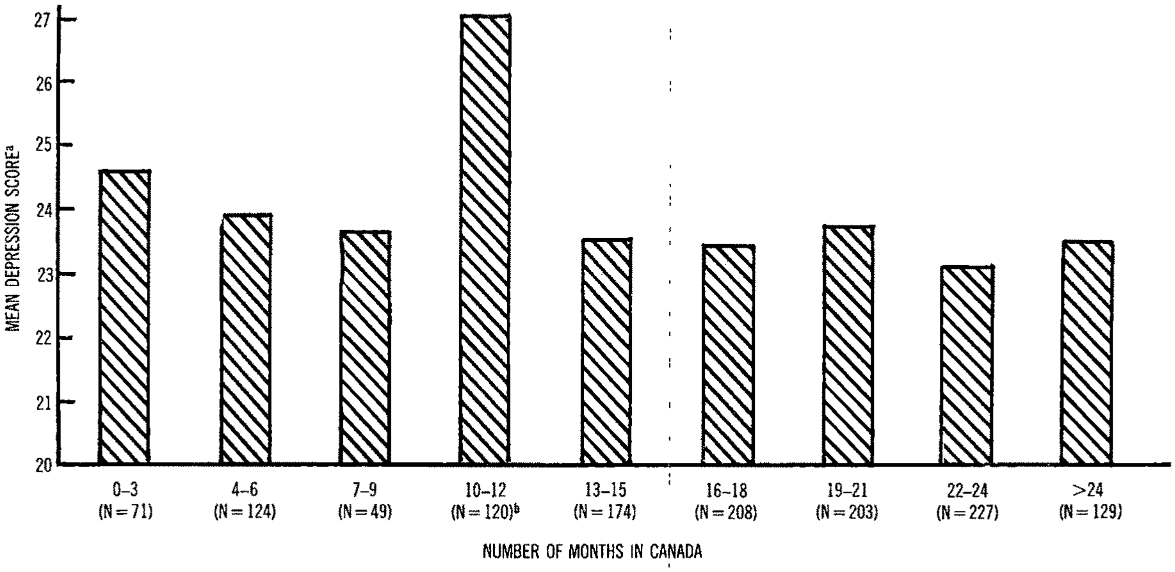
In addition, since community studies (24–26) have established important age and sex effects on rates of mental disorder, we also considered these two variables in our analyses.

RESULTS

Figure 1 shows the depression scores of the subjects grouped according to the length of time they had been in Canada when first interviewed. The depression scores differed significantly among these groups ($F=4.5$, $df=8, 1296$, $p<0.001$). Student-Newman-Keuls post hoc comparisons reveal that those who had been living in Canada for 10–12 months at the time of the survey scored significantly higher on the depression scale than any of the others.

Sociodemographic characteristics played a role in determining when refugees were admitted to Canada. For example, resettlement officers were likely to select intact families sooner than single individuals. If family type were to prove a determinant of mental health status, then any relationship observed between time since arrival and depression might be spurious, due to

FIGURE 1. Relationship Between Depression and Length of Time in Canada for 1,305 Southeast Asian Refugees



[a]A higher score indicates more depression. Significant difference among groups (F=4.5, df=8, 1296, $p<0.001$).
[b]Significantly higher than all other groups ($p<0.05$, Student-Newman-Keuls post hoc comparisons).

the fact that the group who had been in Canada for 10–12 months contained a high proportion of unattached people rather than because of any effect of time in the country on mental health adjustment. To establish the stability of the relationship between time since arrival and depression, we performed a multiple regression analysis controlling for four potentially confounding variables—family type, ethnicity, age, and sex. We first entered these four control variables; then, in a second step, we entered time since arrival. Because the effect of time since arrival is not linear, we dichotomized this variable, comparing the subjects who had been in Canada for 10–12 months with all the others.

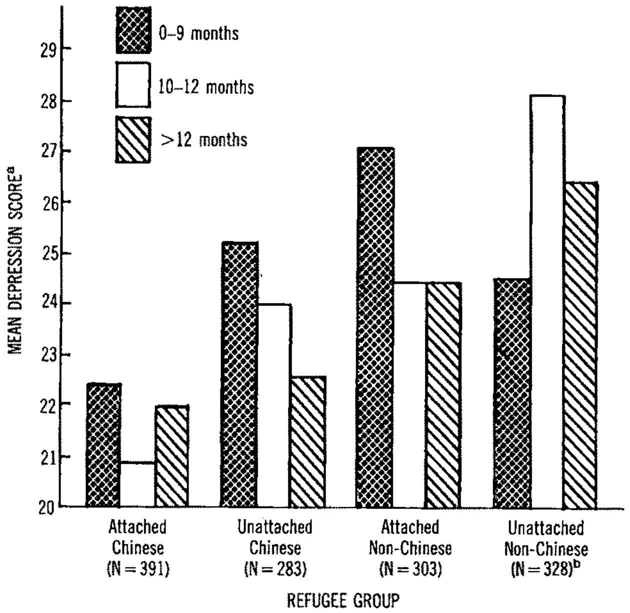
In the first step of the two-step multiple regression analysis of the control variables of family type, ethnicity, age, and sex, the multiple r was 0.34, the cumulative r^2 was 0.11, and the increment in r^2 was 0.11 (F=41.9, df=4, 1300, $p<0.001$). In step two, analyzing the variable of length of time in Canada, the multiple r was 0.35, the cumulative r^2 was 0.12, and the increment in r^2 was 0.007 (F=10.4, df=1, 1299, $p<0.001$). Taken together, the five variables exerted a significant effect on depression (F=35.8, df=5, 1299, $p<0.001$), together explaining 12.1% of the variance in depression scale scores. By themselves, the four control variables accounted for 11% of the total variance in depression scores. Ethnicity and family type made significant contributions to explaining the variance in mental health scores when all other variables were simultaneously controlled (family type beta=0.12, $p<0.001$; ethnicity beta=0.25, $p<0.001$). With ethnicity and family type controlled, age and sex had no effect on depression. Adding the time since arrival variable increased the explanatory power of the predictive equation by 1%.

Ethnicity, family type, and length of time since arrival in Canada exerted significant, independent contributions to depression scores. However, the analyses presented so far do not address possible interactions among these variables. It is conceivable, for example, that not all refugees experience elevated depression 10–12 months after arrival in Canada but that only certain people are at risk. To explore this issue, we subgrouped the refugees using ethnicity and family type as control variables. To avoid too-small numbers, we collapsed family type into a dichotomous variable—married with spouse here (attached) versus all others (single, widowed, divorced, or forcibly separated) (unattached). The result was four subcategories: attached Chinese (N=391), unattached Chinese (N=203), attached non-Chinese (N=303), and unattached non-Chinese (N=328). (Numbers do not add up to 1,348 because some refugees did not complete the depression scales.) We then examined the effect of length of time in Canada for each refugee subgroup. Once again, to avoid small numbers, we collapsed time periods into 9 months or less since arrival, 10 to 12 months since arrival, and more than 1 year in Canada. In a separate set of analyses, we repeated this procedure, entering age in one set of analyses and sex in a second.

The results of the analysis, presented in figure 2, demonstrate an interaction between ethnicity, family type, and length of time in Canada. Only the unattached non-Chinese who had been in Canada 10–12 months demonstrated an increased risk of depression. Sex and age did not contribute to any interaction effects.

The analyses reported to this point dealt with cross-sectional data and included subjects who had been

FIGURE 2. Relationship Between Depression, Ethnicity, Family Type, and Length of Time in Canada for 1,305 Southeast Asian Refugees



[a] A higher score indicates more depression.

[b] F=4.77, df=2, 325, $p<0.01$; 10–12-month group mean significantly higher than others ($p<0.05$, Student-Newman-Keuls procedure).

living in Canada for varying lengths of time, as an approach to studying the effects of length of time since arrival on psychological adaptation. Longitudinal data, based on the repeat interviews of subjects 24 months after the initial survey, offer another way of examining the question of whether adaptation varies as a function of the length of time a refugee lives in the country of resettlement.

Depression scores in the total sample declined substantially and significantly between the first and second interviews (time 1 mean±SD score=23.5±5.8; time 2 mean score=22.0±5.3) (t=8.2, df=1167, $p< 0.001$). As illustrated in figure 3, each of the "length of residence" subgroups exhibited a reduction in depression between time 1 and time 2. (Two of the 1,169 refugees did not complete the depression scales.) For example, those who had been in Canada for less than 3 months at the initial interview (time 1) had a mean depression score of 24.4; 2 years later, their mean score was 21.1. Figure 3 also suggests a tendency for those who had been in Canada for less than 1 year at time 1 to show the most improvement in depression 2 years later. A repeated-measures analysis of variance (27) revealed that this trend was statistically significant (F=2.05, df=8, 1157, $p<0.05$). The group of unattached non-Chinese who scored particularly high on depression 10–12 months following their arrival in Canada still scored significantly higher than any other group 2 years later: mean±SD depression scores at time 2: attached Chinese=20.9±5.0; unattached Chinese=20.8±4.3; attached non-Chinese=22.7±5.2; unattached non-Chinese=23.8±5.8 (F=22.99, df=3, 1163, $p<0.001$); the score of the unattached non-Chinese was significantly higher than those of the others ($p<0.05$, Student-Newman-Keuls procedure).

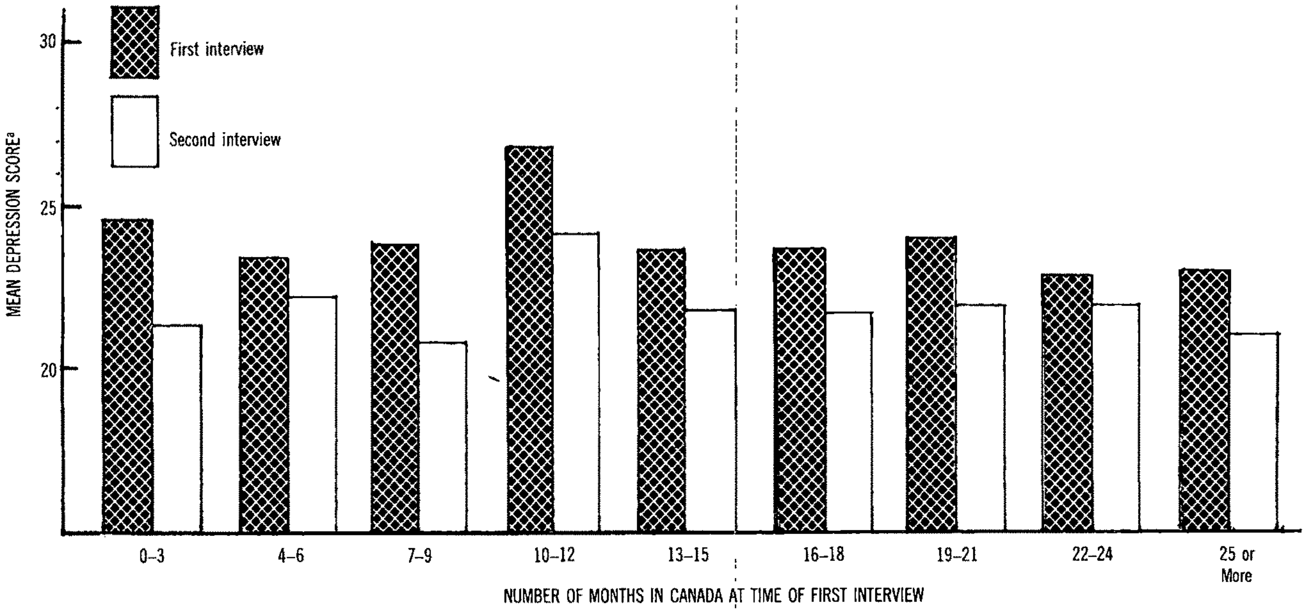
DISCUSSION

The answer to the question, Are certain phases of resettlement characterized by greater mental health risk? must be a qualified yes. As others have already demonstrated (9), refugees experience better mental health the longer they stay in the country of asylum. This effect is particularly marked during the early years of resettlement. However, in our study, refugees who were bereft of family and who did not have access to a like-ethnic community of significant size encountered a high-risk period for depression 10–12 months after arrival.

The construct of "anniversary reactions," described by Pollock (28) in 1970, seems potentially useful to explain both the depression and the timing of this reaction among the most vulnerable groups of refugees. At 10–12 months, unattached non-Chinese, like the bereaved, may be experiencing the anniversary of a profound loss—in the case of the refugees, the loss of Southeast Asia.

These results are consistent with the concept that a period of elevated risk for emotional disorder can be identified during early resettlement. They also shed some light on the disagreements in the literature about when this period occurs. Tyhurst (2, 3) suggested that immigrants are at maximum risk for developing psychological disorder 2–3 months after arrival, but Rumbaut (8) placed the risk period during the second year of resettlement. Since our study used methods similar to those used by Rumbaut, the inconsistency between our finding that mental health risk peaks at 10–12 months after arrival and his data suggesting that it takes place at 12–18 months is most interesting. This inconsistency may be attributable, at least in part, to differences in the circumstances of immigration. For example, although, like Rumbaut, we have dealt with a community sample of Southeast Asia refugees, there are profound differences in the two populations. Our sample, entirely ethnic Chinese, Vietnamese, and Laotian, contained very few Hmong and no Khmer; however, the latter two groups made up almost half of Rumbaut's sample. Were it possible to quantify suffering, most authorities would probably agree that Khmer and Hmong refugees experienced even greater hardships before resettlement than other Southeast Asians (9, 29; unpublished 1977 paper of Aylesworth et al.). Perhaps a terrible past makes present conditions seem tolerable, at least for a while: the worse the past has been, the longer it takes to become disillusioned with the present. Thus, disillusionment and attendant depression may be postponed longer for Hmong and Khmer than for other Southeast Asian refugees.

FIGURE 3. Relationship Between Change in Depression Scores Over 2 Years and Length of Time in Canada for 1,167 Southeast Asian Refugees



^a A higher score indicates greater depression.

Individual time perspective may be another explanatory psychological mechanism. In another publication (30), I presented data suggesting that attending to the present, separating from the past, and refusing to acknoweldge the future is a cognitive coping strategy adopted under states of duress. Under more relaxed conditions, the refugees allow past and future to emerge into consciousness, reestablishing a normative state of "time-bindedness." However, giving up the focus on the present ushers in a period of increased risk of depression. People who have suffered the most hardship may cling the longest to the adaptive pattern of isolating the present from past and future.

Despite the fact that, on the whole, depression declined over time, one group of refugees with particularly few resources who were highly depressed at 10–12 months after arrival still suffered elevated levels of depression 2 years later. Consistent with other research (9), these data suggest that depression in a vulnerable population is not a transient problem. High levels of depressive symptoms place individuals at risk for developing full-blown clinical depression, which in turn has a tendency to become chronic (31, 32). Given the needs and the numbers of immigrants resettling in North America each year, the development of programs to support a healthy adaptation must be assigned a high priority.

One cannot assume that mental health risk is confined to the early years of adaptation. Our own data cover only the first 4 years of resettlement. Perhaps the refugees as a whole, or specific subgroups among them, will experience more mental health risk at some time in the future. Krupinski et al. (33), for example, reported that young immigrant women were relatively resistant to mental health problems for a decade or more after resettlement. However, when they later experienced substantial role losses, their risk of incurring mental disorders increased.

The high-risk groups in our study—the unattached and the non-Chinese—had at least one thing in common: they had little social support. Because there were no resident communities in place in Vancouver, Laotians and Vietnamese could not turn to an ethnic community for support, as their Chinese counterparts could. Having no immediate family available created a situation of double jeopardy for unattached non-Chinese. Most had escaped to Canada with an obligation to send money to their families in the home country and eventually to sponsor their families' resettlement in Canada, an obligation difficult to fulfill if one is—as many of these refugees were—poorly trained, non-English-speaking, and bereft of familiar symbols or community to provide guidance.

Vancouver's large Chinese community created an advantage for the ethnic Chinese refugees. Other unpublished data of our own suggest that Chinese refugees did not enjoy overwhelming advantages in instrumental support, such as help in finding jobs. However, the like-ethnic community provides emotional support by reinforcing one's sense of identity and self-worth, by providing opportunities for friendship, and by mitigating feelings of isolation.

It is possible, of course, to interpret the association between elevated mental health risk, ethnicity, and family status as being due to differences in individual characteristics rather than as reflections of social support. For example, the Chinese, sojourners for many generations in Vietnam, may have come to Canada better equipped to settle as immigrants than the Vietnamese or Laotians who left their native countries. Similarly, people who managed to escape with intact family groups may have done so by virtue of a level of personal resourcefulness not attained by others who left Southeast Asia as individuals.

Nature versus nurture questions cannot be definitively answered by data like ours. However, efforts to help refugees through early resettlement cannot be postponed until definitive answers emerge. Our findings, which are consistent with those of many other studies suggesting that the support of the like-ethnic community assumes crucial importance during early phases of resettlement (34, 35), provide a strong argument for programs designed to bolster such support. For example, from 1979 to 1981, Canadian government resettlement policy concentrated on distributing refugees across the country in numbers proportional to the populations of the 10 provinces. Since no attention was paid to refugee ethnicity, the small numbers of immigrating Laotians, Vietnamese, and Cambodians became widely dispersed. If future resettlement policy were to take into account the importance of the ethnic community and the supportive potential of self-help groups (34, 35), the promotion of successful adaptation might be better accomplished. Likewise, family reunification programs are important, not only on humanitarian grounds but also as a way of combating isolation—particularly in cultural groups such as the Southeast Asians, which emphasize the family so strongly.

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Atenolol in Seasonal Affective Disorder: A Test of the Melatonin Hypothesis

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To test the hypothesis that the antidepressant effects of bright light in seasonal affective disorder are mediated by the suppression of melatonin, 19 patients with this disorder were given atenolol, which suppresses melatonin secretion, and placebo in a double-blind crossover study. No difference in antidepressant efficacy was found between drug and placebo in the sample as a whole, which argues against the melatonin hypothesis of phototherapy. However, in three of the patients atenolol provided repeated, marked, and sustained relief of symptoms, suggesting that it may be useful in treating the winter depressive symptoms of some patients with seasonal affective disorder.

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Seasonal affective disorder is a condition in which the symptoms exhibit a characteristic annual pattern (depression in fall and winter and euthymia or hypomania in spring and summer) (1). These changes are reminiscent of the seasonal rhythms in behavior commonly found among animals (2). Just as seasonal rhythms in animals can be changed by modifying patterns of exposure to environmental light (3), so can the symptoms of winter depression be ameliorated by exposing patients with seasonal affective disorder to bright environmental light during the winter (1, 4–9). The use of bright (2500 lux) light was initially inspired by the finding of Lewy et al. (10) that such light was capable of suppressing nocturnal melatonin secretion in humans, whereas ordinary room light was not. In a similar fashion we have shown in several studies (1, 4, 5) that bright light is capable of producing powerful antidepressant responses in patients with seasonal affective disorder, whereas dim light (300 lux or less) is not. These observations led us to hypothesize that, just as melatonin is important in mediating the seasonal response to photoperiod in many other species (11), changes in the pattern of melatonin secretion might be responsible for the seasonal changes in patients with seasonal affective disorder. We suggested further that the effects of bright light on melatonin secretion might be responsible for its antidepressant properties (12).

One way to test this hypothesis would be to administer a drug that mimics the effects of light on melatonin secretion and to evaluate whether such a drug has antidepressant effects in seasonal affective disorder. Besides the direct suppressant effect of bright light on melatonin that we have mentioned, there are data which suggest that bright light is also capable of influencing the timing of the nocturnal rise and diurnal fall in melatonin secretion (8). Which specific property of melatonin secretion is critical for mediating the seasonal effects of photoperiod has not been fully ascertained for most species. However, in two species in which this has been well studied—sheep (13) and Djungarian hamsters (14)—the duration of melatonin secretion is the critical seasonal time cue. These observations led us to hypothesize that, if melatonin secretion is in fact important in inducing the symptoms of seasonal affective disorder, then perhaps bright light produces remissions by suppressing melatonin secretion for part of the night, thereby decreasing its duration.

The nocturnal secretion of melatonin can be suppressed pharmacologically by means of β-adrenergic antagonists. Melatonin is ordinarily released from the pineal gland in response to the stimulation of β-adrenergic receptors on the surface of pinealocytes, which are outside the blood-brain barrier (15). The long-acting β-adrenergic antagonist atenolol has been shown to suppress the nocturnal secretion of melatonin in humans when administered in the afternoon hours (16). Peak levels of atenolol appear in the blood within 2–4 hours after ingestion, its elimination half-life is approximately 6–7 hours, and its β-blocking effect persists for at least 24 hours (*Physicians' Desk Reference*). Atenolol appeared to be a good choice of drug for the present study because it is relatively lipid-insoluble and does not readily cross the blood-brain barrier (17). Thus, any observed behavioral effects would be less likely to be the result of a direct effect on the brain than of a peripheral action, such as

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the suppression of melatonin. In this study we tested the hypothesis that the antidepressant effects of bright light in seasonal affective disorder are due to suppression of melatonin secretion by administering atenolol to seasonal affective disorder patients in the late afternoon. In doing so we also evaluated the clinical efficacy of atenolol in the treatment of this condition.

METHOD

Subjects were recruited by means of a newspaper article or were referred by local therapists. In order to be admitted into the program they were required to meet the criteria for seasonal affective disorder of Rosenthal et al. (1), namely, a lifetime history of major depression according to the Research Diagnostic Criteria (RDC) (18), recurrent episodes of fall and winter depression (at least two during consecutive winters) that remitted during the spring and summer, no other *DSM-III* axis I psychiatric disorder, and no clear-cut psychosocial explanations for their seasonal mood changes. Patients were excluded from the study if they were not in reasonably good medical health or if they had specific contraindications for the use of atenolol, such as low blood pressure or asthma. All patients who participated in the study provided informed consent.

Once admitted into the program, patients were followed regularly in an outpatient clinic. Their mood was evaluated by means of the 21-item Hamilton Rating Scale for Depression (19) and a seven-item supplement specifically designed to evaluate atypical symptoms that are characteristic of seasonal affective disorder and other forms of bipolar illness (20). Ratings were made by two raters blind to the patients' treatment status, and a single consensus rating was obtained. When the total Hamilton depression score (excluding the supplement) reached 14 or more for 2 consecutive weeks, the drug study was initiated. Patients were randomly assigned to either atenolol, 100 mg, or placebo in identical capsules administered once daily at 4:00 p.m. for a week. This was followed by a week of withdrawal, the alternate treatment for the next week, and a final week of withdrawal. Patients were rated on the last day of each treatment week. A score of at least 10 on the Hamilton scale was required for admission into the second treatment condition. Both the minimum Hamilton entry scores (14 and 10) and the duration of treatment (1 week) were the same as those used by our group in phototherapy studies of seasonal affective disorder (1, 4, 5, 9).

Pulse and blood pressure (sitting and standing) were measured on days 1, 3, and 7 of each treatment week. If the pulse rate fell below 60 beats/minute or if patients experienced symptomatic postural hypotension, they were evaluated clinically and a decision was made about whether the drug should be discontinued. Patients were asked to complete a side effects checklist at the end of each week of treatment. At the same time they were asked whether they thought they had been taking atenolol or placebo capsules and how sure they were of their guess. After the final week of withdrawal, while the patients were still blind to their treatment conditions, each patient was offered the opportunity to resume treatment with whichever capsule had been found to be most helpful or to receive another type of treatment. Patients continued to be rated on a weekly basis during this informal part of the study.

During each week of the study two 24-hour urine collections were made and the quantity of the major melatonin metabolite 6-hydroxymelatonin sulfate secreted per 24-hour period was determined by the radioimmunoassay method of Arendt et al. (21). Results of the Hamilton mood ratings were analyzed by analysis of variance (ANOVA) with one grouping factor (sequence of administration) and two repeated measures (atenolol versus placebo and pretreatment versus posttreatment). Similar analyses were performed on pulse, blood pressure, and 6-hydroxymelatonin sulfate measurements. Correlations between Hamilton scale change scores and the melatonin metabolite values for both atenolol and placebo conditions were also done.

RESULTS

Twenty-two patients (19 women and three men) with seasonal affective disorder entered the study. The mean±SD age of the sample was 38.7±7.9 years; the mean age at onset was 20.2±8.1 years. All patients met lifetime RDC for major depression with hypomania (bipolar II), except for one patient who had a history of recurrent unipolar depression. Three patients failed to complete the course of treatment: one developed symptomatic hypotension while taking atenolol, one failed to comply with the first treatment condition (atenolol), and one did not relapse following withdrawal of the first treatment condition (atenolol).

The mean±SD reduction in Hamilton scores following atenolol treatment was 6.3±9.5 points, compared with 5.1±9.9 points following administration of placebo capsules. An ANOVA revealed a significant treatment effect for both treatment conditions, with no superiority of atenolol over placebo for the group as a whole (see table 1). Analysis of the supplementary Hamilton depression items yielded similar results. In general, the active drug was well tolerated, and there was no statistically significant difference in side effects between the atenolol and the placebo conditions. However, there was a significant reduction in pulse rate and blood pressure in the atenolol condition compared with the placebo condition (see table 2). The urinary excretion of 6-hydroxymelatonin sulfate was significantly lower in the atenolol condition than with placebo (see table 2). There was no correlation between the lower 6-hydroxymelatonin sulfate secretion and the change in Hamilton mood ratings. Analysis of patients' opinions showed that 10 of 18 patients guessed correctly when given atenolol (one missing

TABLE 1. Hamilton Depression Scores of 19 Patients With Seasonal Affective Disorder Given Atenolol or Placebo in a Crossover Design[a]

	Hamilton Score With Atenolol			Hamilton Score With Placebo		
Patient	Baseline	Treatment	Withdrawal	Baseline	Treatment	Withdrawal
Atenolol first						
1	15	16	27	27	7	0
2	27	22	9	26	23	16
3	15	17	12	24	12	15
4	28	6	24	24	29	—
5	28	1	18	18	23	18
6	14	10	15	15	20	19
7	30	22	23	23	18	12
8	26	4	16	16	20	17
9	27	20	17	17	14	15
Placebo first						
10	23	31	23	19	22	23
11	18	15	22	24	22	18
12	25	23	27	31	9	25
13	20	20	21	18	21	20
14	30	25	18	38	22	30
15	24	31	14	27	7	24
16	12	8	6	17	15	12
17	22	7	12	25	20	22
18	24	12	20	21	3	24
19	19	16	30	28	35	19
All patients						
Mean	22.5	16.2	18.6	23.1	18.0	18.4
SD	5.6	8.7	6.4	5.9	8.0	6.6

[a] Significant difference between atenolol and placebo in treatment effect (F=21.18, df=1, 18, p<0.001); nonsignificant interaction between treatment and condition (F=0.13, df=1, 18, p<0.73).

TABLE 2. Effects of Atenolol and Placebo on Blood Pressure, Pulse, and Urinary Excretion of 6-Hydroxymelatonin Sulfate of 19 Patients With Seasonal Affective Disorder

	Baseline		Atenolol		Placebo		Difference Between Atenolol and Placebo	
Measure	Mean	SD	Mean	SD	Mean	SD	t (df=18)	p
Blood pressure (mm Hg)								
Lying down								
Systolic	122	13	113	13	121	11	5.6	<0.03
Diastolic	72	10	67	11	72	9	4.1	<0.01
Standing								
Systolic	126	15	119	11	124	12	8.4	<0.001
Diastolic	79	12	70	16	79	11	9.6	<0.001
Pulse (beats/minute)								
Lying down	70	9	61	7	69	10	17.2	<0.001
Standing	79	11	68	10	77	10	10.1	<0.001
Urinary 6-hydroxymelatonin sulfate (mg/24 hours)	—	—	3.9	1.1	10.1	3.4	3.1	<0.01

value) and nine of 15 patients guessed correctly when they were given placebo (four missing values). Since patients were aware of the crossover design of the study, the group was divided into those who guessed correctly both times and those who guessed incorrectly both times. There was no significant correlation between the patients' degree of certainty that they were taking the active drug and their degree of antidepressant response as measured by the Hamilton depression scale (Spearman's correlation).

After the formal crossover study was completed, nine patients, while still blind to their treatment conditions, chose to resume treatment with atenolol, which they believed had helped them. Of these nine patients, five responded to treatment with atenolol a second time, with a median reduction in Hamilton score of 15 points. Three of these patients chose to continue to take atenolol for extended periods with continued beneficial effects. During the next two winters these three patients requested that they be treated again with atenolol, and they again reported antidepressant effects throughout the winter months. There was no difference in clinical or demographic details between atenolol responders and nonresponders. There was some difference in time course of response in the three patients who continued to take atenolol: one patient responded within 2–4 hours and the other two between 2 and 3 days of starting to take atenolol. One patient found that he had to take his medicine between 5:00 p.m. and 7:30 p.m. in order to observe a clinical effect. In the other two cases the timing of administration did not appear to be critical.

After the crossover study was completed, two patients, while still blind to the study conditions, requested that they be allowed to return to placebo capsules, which they believed had been helpful. One of these patients remained symptom free but did not think that it was because of the capsules. Of the eight patients who chose not to restart either atenolol or placebo, recovery occurred spontaneously in two patients, after traveling south in three patients, and following phototherapy in two patients. For the one patient who remained depressed despite phototherapy, adjunctive antidepressants were added with moderately beneficial results.

DISCUSSION

The results of this study address three questions: first, whether the antidepressant effects of light are mediated by the suppression of melatonin secretion (12); second, whether atenolol might be a clinically useful treatment for seasonal affective disorder; and third, the degree to which the antidepressant effects of light in earlier studies of seasonal affective disorder might have been mediated by the placebo effect. We will discuss these questions in turn.

1. The melatonin hypothesis. The significant reduction in pulse rate and blood pressure during the atenolol condition indicates that peripheral β-adrenergic blockade did in fact occur. Similarly, the significantly lower excretion of 6-hydroxymelatonin sulfate suggests that atenolol suppressed melatonin secretion. Since atenolol did not show an antidepressant effect significantly superior to that of placebo in the sample as a whole, it appears that suppression of melatonin is an unlikely explanation for the antidepressant effects of light in seasonal affective disorder.

This conclusion is compatible with the finding of Wehr et al. (9) that bright light which was administered to seven patients with seasonal affective disorder at a time of day when melatonin is not being secreted, and which did not suppress melatonin, nonetheless produced significant antidepressant effects. Similarly, Jacobsen and colleagues (unpublished work, 1986) found that 2 hours of bright light treatment given during the middle of the day, when melatonin is not normally secreted, produced clinically significant antidepressant effects in 16 outpatients with seasonal affective disorder. Recently Thompson et al. (22) found that 4 hours of bright light in the middle of the day had more pronounced antidepressant effects than an equivalent amount of light applied in such a way as to extend the photoperiod and suppress melatonin secretion.

We should note that whereas atenolol administration suppresses melatonin secretion, it may not reproduce all the effects of light treatment on melatonin secretion. Thus, the results of this study do not rule out the possibility that bright light treatment might exert its antidepressant effects in seasonal affective disorder by some effect on melatonin secretion other than direct suppression. For example, bright light is capable of altering the timing of melatonin secretion (8). Arendt and Broadway (23) recently suggested that it may be the timing rather than the length of melatonin secretion that serves as a critical influence on seasonal behavior responses in humans, and Lewy et al. (24) emphasized timing as an important factor in the efficacy of phototherapy.

Other studies of the role of melatonin in seasonal affective disorder have also failed to support the hypothesis that melatonin plays a critical role in the pathogenesis of the disorder and in the response to phototherapy, even though they have not ruled out the possibility that melatonin may have some influence on the symptoms of the disorder. For example, the administration of oral melatonin to eight patients who had been treated successfully with bright light therapy reversed some, but not all, of the antidepressant effects of light (12). Preliminary studies have failed to show a difference in melatonin secretion patterns between patients with seasonal affective disorder and normal subjects either in summer or in winter (Sack et al., unpublished work, 1986).

As we have noted, melatonin plays a critical role in seasonal rhythms of reproduction in many species (11). However, there are other types of seasonal rhythms in animals, for example, seasonal rhythms of energy utilization in hamsters, where melatonin is only one of several influences (25). Most of the available evidence suggests that melatonin may play some role in the pathogenesis of seasonal affective disorder but that it is not a critical role. If this is the case, we should perhaps regard certain animal models, such as seasonal rhythms of energy utilization and weight in hamsters, as more useful for our understanding of the pathogenesis of seasonal affective disorder and the mechanism of action of phototherapy than seasonal rhythms of reproduction.

2. Possible clinical utility of atenolol. It is important to note that although there was no overall difference between the antidepressant effects of atenolol and placebo in the present study, a small subgroup of patients experienced considerable antidepressant effects when treated with atenolol. It is also noteworthy that after the formal crossover study was complete, nine patients chose to go back to taking atenolol, whereas only two patients chose to go back to placebo. This preference may reflect some subjective awareness in these patients that atenolol was superior, which was not detected on the formal ratings. The three subjects with the most convincing clinical response to atenolol relapsed when treatment was discontinued, benefited again when it was resumed, requested atenolol the following winter, and reported further beneficial results over an extended period.

Our clinical observations could be explained in several ways. First, they may have been due to a placebo effect. Second, melatonin may have been responsible for depressive symptoms in those who responded. Finally, some other mechanism, as yet undefined, may have been involved. While β blockers have been reported to have therapeutic effects in patients with anxiety states and panic disorder (26, 27), we should note that in the three atenolol responders, the therapeutic effects of the drug were observed for a wide range of depressive symptoms and not only for those reflecting anxiety.

3. The placebo effect. The results of this study may further our understanding of the placebo effect in the treatment of patients with seasonal affective disorder by phototherapy. Because such treatment studies cannot be carried out in a double-blind fashion, the question of whether all observed antidepressant effects have been due to placebo responses has concerned researchers in the field. Since the present study is the first double-blind drug study of patients with seasonal affective disorder, their response to placebo capsules is of particular interest. The statistically significant placebo effect represented a mean drop of 5.1 points on the Hamilton depression scale. This change is slightly higher than the responses we observed previously to treatment with "control" lighting conditions in studies of phototherapy, but it is considerably smaller than the changes we saw following treatment with bright light (28). The results of this study suggest that people with seasonal affective disorder, like other patients, respond favorably to nonspecific placebo elements in a treatment study. However, the large discrepancy between the placebo effect seen here and the marked effects of phototherapy reported in earlier studies suggests that the phototherapy either has specific antidepressant effects or is an extraordinary placebo.

In conclusion, the overall lack of antidepressant efficacy of atenolol in the treatment of seasonal affective disorder does not support the hypothesis that the suppression of melatonin secretion is the mechanism of action of phototherapy in most patients with seasonal affective disorder. This corroborates other evidence that melatonin secretion is not of pivotal importance in the pathogenesis of seasonal affective disorder (12). However, in a few patients atenolol proved to be extremely helpful in treating the winter depressive symptoms of seasonal affective disorder, although the mechanism of action of this effect remains unknown.

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A Family Study of the Subtypes of Schizophrenia

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The authors conducted a blind family study based on probands diagnosed as schizophrenic by DSM-III *and subtyped by four diagnostic systems. The pattern of psychopathology in relatives did not differ as a function of the probands' subtype diagnosis. Relatives of paranoid and nonparanoid schizophrenic probands had similar risks for schizophrenia and affective illness. Resemblance in subtype diagnosis between probands and their affected relatives did not exceed chance expectation. The etiologic role of familial factors appears to be similar in each of the traditional subtypes of schizophrenia. No evidence was found for familial factors specific for individual subtypes.*

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Since its inception as a diagnostic entity, attempts have been made to divide schizophrenia into homogeneous subgroups (1, 2). The first and most enduring of the approaches to this problem was taken by Kraepelin when he divided dementia praecox into hebephrenic, catatonic, and paranoid forms (1). Since then, every major nosologic system in psychiatry has included these "traditional" subtypes of schizophrenia (3).

We have previously examined the reliability (4), outcome (5), and stability (6) of the four current major Anglophonic systems for subtyping schizophrenia: *DSM-III*, Research Diagnostic Criteria (RDC) (7), *ICD-9* (8), and the criteria of Tsuang and Winokur (9). In this final report of the series, we examine these subtyping systems from a familial perspective.

We sought answers to three questions regarding these subtyping systems: Is the risk for schizophrenia and schizophrenia-like disorders different in relatives as a function of the subtype of the proband? Does the pattern of nonschizophrenic illness differ in relatives of probands with differing subtypes? Is there a resemblance for the subtype of schizophrenia between probands and their affected relatives?

METHOD

Probands for this study were selected from 510 patients consecutively admitted to the Iowa Psychopathic Hospital from 1934 to 1944 with a chart diagnosis of schizophrenia (10). On the basis of their index hospital chart (patients from the "Iowa 500" study) or their index chart and follow-up material (patients from the "Iowa non-500" study), 332 of these patients met *DSM-III* criteria for schizophrenia. For 271 (81.6%) of these probands, the index admission was their first psychiatric hospitalization.

In this patient cohort, the subtypes of schizophrenia are only modestly stable over time (6). In probands of this family study, the subtypes of schizophrenia were examined early in the course of illness (i.e., based on the index chart for probands from the Iowa 500 series and the index chart plus short-term follow-up information—sometimes needed to make a *DSM-III* diagnosis of schizophrenia—for probands from the Iowa non-500 series). This was done because in the initial phases of illness 1) the clinical manifestations of the subtypes of schizophrenia are usually clearest and 2) the proportion of patients with a specific subtype diagnosis is highest (6), thereby maximizing statistical power.

A subtype diagnosis was assigned only if the proband met criteria for schizophrenia in the "parent" diagnostic system (which for the Tsuang-Winokur criteria was the Washington University criteria [11]). We eliminated probands who had no available relatives, who did not meet criteria for schizophrenia in the parent system, or who were one of the small number assigned a simple, latent, or residual subtype. The following numbers of probands were available in each diagnostic system: *DSM-III*—252, RDC—248, *ICD-9*—243, and Tsuang-Winokur—243.

First-degree relatives of these probands and matched

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surgical control subjects were personally interviewed with a structured psychiatric interview (12) by raters who were blind to the relationship between the relative and the proband. In addition, the public psychiatric hospitals of Iowa were searched for records for these identified relatives. Of the total of 723 evaluated relatives, 640 had only been personally interviewed, 28 had both a personal interview and a hospital record, and 55 had a hospital record only. Using *DSM-III*, two of us (K.S.K. and A.M.G.), who were blind to proband status, diagnosed the relatives, with high interrater reliability (10). We present results for all 723 evaluated relatives. While this approach probably produces an upward bias on morbid risk estimates, it uses all the available information (10).

The age-corrected morbid risks, calculated by either the Stromgren or abridged Weinberg method, are based on broadly defined primary diagnoses (10). Because of prior evidence, we created a superordinate diagnostic category of "all nonaffective psychotic disorders"; it included the following *DSM-III* categories: schizophrenia, schizophreniform disorder, schizoaffective disorder, paranoid disorder, and atypical pyschosis. For consistency, the subtype termed "disorganized" in *DSM-III* and RDC was termed "hebephrenic," and the subtype called "undetermined" by the Tsuang-Winokur criteria was called "undifferentiated."

The following approach was used in analyzing the morbid risk data. First, for each diagnostic category we performed an N×2 chi-square analysis of the risk in relatives, where N is the number of subtype categories in the probands. Second, because of strong a priori evidence, we specifically tested, by 2×2 chi-square analysis, the difference in risk for all disorders in relatives of paranoid versus nonparanoid probands (13) and for affective illness only in relatives of catatonic versus noncatatonic probands (14). The p values reported are two-tailed.

The concordance of subtypes between probands and their affected relatives was assessed by the kappa statistic (15). Pairs were analyzed in which neither proband nor relative had a diagnosis of residual, latent, or simple schizophrenia. To correct results for unreliability, the kappa values were divided by those found for interrater reliability (6).

The power of the proposed comparisons can be assessed by the noncentral chi-square distribution (16), assuming a two-tailed p value of 0.05. In a comparison of relatives of paranoid and nonparanoid probands diagnosed by *DSM-III* criteria, power will exceed 50% when the risk for schizophrenia is approximately three times greater in relatives of nonparanoid probands. For all nonaffective psychotic disorders, power is approximately 50% to detect a twofold and 75% to detect a threefold difference in risk. Power is approximately 60% and 75% to detect a 1½-fold and twofold excess, respectively, of affective illness in relatives of paranoid schizophrenic probands. Given the observed sample size and probability of chance agreement, uncorrected kappa values for *DSM-III* subtypes in probands and affected relatives would have to exceed 0.30 to reach statistical significance.

RESULTS

Tables 1–3 present the age-corrected (or morbid) risks for *DSM-III* disorders in first-degree relatives of schizophrenic probands subtyped according to *DSM-III*, *ICD-9*, and Tsuang-Winokur criteria, respectively. (Results for probands subtyped by RDC, which were very similar to those found with *DSM-III* criteria, are not presented here.)

Three results are noteworthy. First, no significant difference in the risk for either schizophrenia alone or for all nonaffective psychotic disorders was seen in relatives as a function of the subtype diagnosis of the proband. Although not statistically significant, a trend was found in all systems for the risk for these disorders to be *higher* in relatives of paranoid versus nonparanoid schizophrenic probands.

Second, no significant difference was found in the risk for affective disorders in relatives of schizophrenic probands subtyped by the various diagnostic systems. According to *DSM-III* and *ICD-9* criteria, relatives of catatonic schizophrenic probands were at a higher risk for affective disorder, but these differences were not significant ($\chi^2=1.23$, df=1, p=0.26, and $\chi^2=0.46$, df=1, p=0.50, respectively).

Third, no significant difference was found in the risk for either anxiety disorders or alcoholism in relatives as a function of the proband's subtype diagnosis. However, there was a trend in all diagnostic systems for anxiety disorder to be less common in relatives of paranoid versus nonparanoid schizophrenic probands. This difference reached marginal levels of statistical significance with the *ICD-9* criteria (table 3).

Either uncorrected or corrected for diagnostic unreliability, the agreement in subtype diagnoses between probands and their schizophrenic relatives was consistently positive but did not exceed chance expectation in any diagnostic system (table 4).

DISCUSSION

This study sought to answer three questions regarding the familial contribution to the etiology of subtypes of schizophrenia. We will begin by discussing each of these in turn.

Schizophrenia in Relatives

The first question addressed was whether the risk for schizophrenia (or all nonaffective psychotic disorders) differed in relatives as a function of the schizophrenic subtype of the proband. In 1981 Kendler and Davis (13) noted nine studies that examined the risk for schizophrenia in relatives of schizophrenic probands

TABLE 1. Morbid Risk for Psychiatric Disorders in Relatives of Schizophrenic Probands Subtyped by *DSM-III* Criteria

	Proband Subtype				Chi-Square Analysis			
					All Subtypes (df=3)		Paranoid Versus Nonparanoid (df=1)	
Variable	Paranoid	Hebephrenic[a]	Catatonic	Undifferentiated	χ^2	p	χ^2	p
Number of probands	68	50	13	121				
Number of relatives	185	150	37	347				
Morbid risk for psychiatric disorders in relatives[b]								
Schizophrenia					1.36	0.72	0.02	0.90
Morbid risk (%)	3.9	4.8	5.6	3.0				
SE	1.4	1.8	3.9	0.9				
Nonaffective psychotic disorders					6.40	0.09	2.91	0.09
Morbid risk (%)	10.8	10.3	5.7	5.4				
SE	2.4	2.5	4.0	1.2				
Affective disorders					2.19	0.53	0.06	0.80
Morbid risk (%)	6.7	5.1	12.0	7.8				
SE	2.0	1.9	5.6	1.5				
Major depression					3.46	0.32	0.02	0.89
Morbid risk (%)	6.3	3.8	12.2	6.3				
SE	1.9	1.7	5.7	1.4				
Bipolar illness					1.36	0.71	0.73	0.39
Morbid risk (%)	0.6	1.4	0.0	1.6				
SE	0.6	1.0		0.7				
Anxiety disorders					1.92	0.56	1.68	0.20
Morbid risk (%)	1.7	4.1	2.8	3.6				
SE	1.0	1.7	2.8	1.0				
Alcoholism					2.18	0.54	1.09	0.30
Morbid risk (%)	4.6	2.8	0.0	3.3				
SE	1.6	1.4		1.0				

[a] For consistency, the subtype termed "disorganized" in *DSM-III* was termed "hebephrenic."

[b] The number of affected relatives and the total lifetimes at risk used to calculate the morbid risk figures are available from the authors on request. Morbid risk equals, in any given group of relatives, the number of affected individuals divided by the total lifetimes at risk.

divided into subtypes. Five of these studies found that the relatives of paranoid schizophrenic probands had a significantly lower risk for schizophrenia than did relatives of nonparanoid schizophrenic probands, while four found no significant variation in risk of schizophrenia in relatives of probands with different subtypes. Since then, one family history study (17) found a significantly higher risk for schizophrenia in relatives of paranoid versus nonparanoid schizophrenic patients. The large variation in methodology of these earlier investigations, including major differences in the "criteria" for subtyping, makes discrepancies in results difficult to interpret.

In the present study, neither the risk for schizophrenia nor the risk for all nonaffective psychotic disorders differed in relatives of probands with the various subtypes of schizophrenia. This finding was consistent in all four subtyping systems and suggests that the magnitude of the familial contribution to liability to illness is similar for all of the classic subtypes of schizophrenia. Specifically, our results are not consistent with previous claims that paranoid schizophrenia represents, from a familial perspective, a "mild" form of schizophrenia (13). The present results are similar to those found in a previous study that used blind consensus clinical diagnoses of schizophrenic probands and relatives from the Iowa 500 study (18). However, an earlier report based only on chart family history information, from the same study, found the risk for schizophrenia to be considerably higher in relatives of nonparanoid versus paranoid schizophrenic probands (19). If any trend was evident from the current investigation, which was based on a larger sample size and more rigorous methodology, it was for higher, not lower, risks for schizophrenia or all nonaffective psychotic disorders in relatives of paranoid versus nonparanoid schizophrenic probands.

Other Psychiatric Disorders in Relatives

The second major question addressed by this report was whether the pattern of nonschizophrenic psychopathology differed in families as a function of the schizophrenic subtype of the proband. Such a difference might be evidence for the etiologic heterogeneity of the subtypes of schizophrenia. For example, it has been suggested that catatonic (20) or paranoid (21) schizophrenia may be etiologically related to affective illness. If this were true, then relatives of probands with these subtypes should have a higher risk for affective disorder. Consistent with the few previous studies that addressed this question (13), no evidence was found in any diagnostic system for a higher risk for affective illness in relatives of paranoid versus nonparanoid schizophrenic probands. Furthermore, the risk for affective illness in relatives of paranoid

TABLE 2. Morbid Risk for Psychiatric Disorders in Relatives of Schizophrenic Probands Subtyped by Tsuang-Winokur Criteria

				Chi-Square Analysis			
	Proband Subtype			All Subtypes (df=2)		Paranoid Versus Nonparanoid (df=1)	
Variable	Paranoid	Hebephrenic	Undetermined	χ^2	p	χ^2	p
Number of probands	33	83	127				
Number of relatives	89	231	371				
Morbid risk for psychiatric disorders in relatives[a]							
Schizophrenia				3.39	0.18	3.19	0.07
Morbid risk (%)	6.9	2.6	3.3				
SE	2.7	1.1	1.0				
Nonaffective psychotic disorders				2.38	0.30	2.29	0.13
Morbid risk (%)	11.8	6.7	7.4				
SE	3.5	1.7	1.4				
Affective disorders				2.41	0.30	0.45	0.50
Morbid risk (%)	5.0	5.2	8.3				
SE	2.4	1.5	1.5				
Major depression				1.28	0.53	0.04	0.84
Morbid risk (%)	5.1	4.3	6.6				
SE	2.5	1.4	1.4				
Bipolar illness				1.98	0.37	1.48	0.22
Morbid risk (%)	0.0	0.9	1.8				
SE		0.6	0.7				
Anxiety disorders				1.70	0.43	1.39	0.24
Morbid risk (%)	1.2	3.1	4.0				
SE	1.2	1.2	1.0				
Alcoholism				1.37	0.50	1.19	0.28
Morbid risk (%)	4.7	2.2	2.8				
SE	2.3	1.0	0.9				

[a] The number of affected relatives and the total lifetimes at risk used to calculate the morbid risk figures are available from the authors on request. Morbid risk equals, in any given group of relatives, the number of affected individuals divided by the total lifetimes at risk.

schizophrenic probands closely resembled that found in relatives of surgical control subjects (10). Because of small numbers, previous reports of a familial link between catatonic schizophrenia and affective disorder could not, with confidence, be confirmed or denied. With the possible exception of catatonic schizophrenia, the present study revealed no evidence that the subtypes of schizophrenia were, from a familial perspective, etiologically heterogeneous.

Subtype Concordance Between Probands and Their Affected Relatives

The third major question addressed in this report was whether probands and their schizophrenic relatives resembled one another in their subtype diagnosis. If familial factors influence the liability to *specific* subtypes of schizophrenia, then the subtype diagnoses in affected relatives should be correlated. Previous results in this area have been conflicting. Of 10 previous family studies, five found evidence for significant subtype resemblance in pairs of affected relatives, while five did not (13, 17). However, all three studies examining pairs of monozygotic twins concordant for schizophrenia found substantial subtype resemblance (13).

In this report, although agreement in the subtype diagnosis between probands and their affected relatives was modestly positive in all diagnostic systems, it never exceeded chance expectation. It is possible that larger sample sizes might have revealed significant findings. However, the results of this investigation are consistent with the following hypothesis: familial factors strongly affect an individual's liability to develop the syndrome of schizophrenia (10) but do not greatly influence the specific subtype that will emerge.

Methodologic Limitations

The results of this investigation should be interpreted in the context of its methodologic strengths and limitations. The strengths of the sample include personal interviews with relatives and blind and reliable diagnoses based on operationalized criteria (10). The number of relatives of schizophrenic probands in this study was large; however, despite the large number of relatives, cases of psychotic illness were not extremely common. Therefore, only large differences in risk for these disorders across groups of relatives had a high probability of detection.

An important methodologic limitation of any study of the subtypes of schizophrenia is the instability of subtype diagnoses. Subtypes of schizophrenia are only modestly stable over time (6). Furthermore, over time, the subtypes tend to change from specific (e.g., paranoid, hebephrenic, and catatonic) to nonspecific (e.g., undifferentiated and residual) forms. Therefore, the results of a study of subtypes of schizophrenia could be expected to vary as a function of when in the course of their illness the patients were examined.

TABLE 3. Morbid Risk for Psychiatric Disorders in Relatives of Schizophrenic Probands Subtyped by *ICD-9* Criteria

				Chi-Square Analysis			
	Proband Subtype			All Subtypes (df=2)		Paranoid Versus Nonparanoid (df=1)	
Variable	Paranoid	Hebephrenic	Catatonic	χ^2	p	χ^2	p
Number of probands	121	110	12				
Number of relatives	346	310	34				
Morbid risk for psychiatric disorders in relatives[a]							
Schizophrenia				1.38	0.50	0.55	0.46
Morbid risk (%)	4.3	3.0	6.1				
SE	1.2	0.9	4.2				
Nonaffective psychotic disorders				0.98	0.61	0.96	0.33
Morbid risk (%)	8.9	6.9	6.2				
SE	1.7	1.4	4.2				
Affective disorders				0.60	0.74	0.27	0.60
Morbid risk (%)	6.3	7.1	9.8				
SE	1.5	1.5	5.4				
Major depression				1.14	0.57	0.13	0.72
Morbid risk (%)	5.3	5.6	10.0				
SE	1.4	1.3	5.5				
Bipolar illness				0.72	0.70	0.16	0.69
Morbid risk (%)	1.1	1.5	0.0				
SE	0.6	0.7					
Anxiety disorders				3.93	0.14	3.74	0.05
Morbid risk (%)	1.7	4.5	3.1				
SE	0.8	1.1	3.0				
Alcoholism				1.50	0.47	0.11	0.73
Morbid risk (%)	3.1	3.9	0.0				
SE	1.0	1.1					

[a] The number of affected relatives and the total lifetimes at risk used to calculate the morbid risk figures are available from the authors on request. Morbid risk equals, in any given group of relatives, the number of affected individuals divided by the total lifetimes at risk.

TABLE 4. Agreement in Subtype Diagnosis Between Schizophrenic Probands and Their Schizophrenic Relatives Diagnosed With Four Systems[a]

			Kappa			
			Uncorrected		Corrected[b]	
Diagnostic System	N	Concordance (%)	Mean	SE	Mean	SE
DSM-III	22	40.9	+0.13	0.15	+0.20	0.22
RDC	20	40.0	+0.17	0.15	+0.28	0.25
ICD-9	19	52.6	+0.16	0.20	+0.28	0.35
Tsuang-Winokur criteria	24	45.8	+0.12	0.17	+0.16	0.24

[a] For *DSM-III* and RDC, agreement was restricted to proband-relative pairs in which both members were diagnosed as having paranoid, disorganized (hebephrenic), catatonic, or undifferentiated schizophrenia. For *ICD-9*, agreement was restricted to proband-relative pairs in which both members were diagnosed as having paranoid, hebephrenic, or catatonic schizophrenia. For the Tsuang-Winokur criteria, agreement was restricted to proband-relative pairs in which both members were diagnosed as having paranoid, hebephrenic, or undetermined schizophrenia.

[b] Corrected kappa values, obtained by dividing uncorrected values by those found for interrater reliability (4), reflect agreement in subtype between probands and relatives after removal of the effect of unreliability of diagnosis.

In this study, subtype diagnoses were based on the clinical presentation of the probands early in their course of illness. This is the time at which the maximum number of patients meet the criteria for a specific subtype of schizophrenia. By contrast, information was often not available on relatives until late in their course of illness. Of the 26 first-degree relatives of probands diagnosed as schizophrenic, 15 (57.7%) were diagnosed by *DSM-III* criteria as undifferentiated or residual. By comparing the subtypes of probands examined early in their course with those of affected relatives often seen much later, we may underestimate subtype resemblance in relatives. Such a bias would be consistent with the striking similarity of the subtypes of monozygotic twins concordant for schizophrenia (13). Since age at onset is so highly correlated in these twins (22), they are likely to be examined at a similar stage of their illness.

CONCLUSIONS

Although probands with different subtypes of schizophrenia vary considerably in outcome (5), no difference was found in the risk for psychiatric disorders in their relatives, nor did the subtypes tend to "breed true" within families. The subtypes of schizophrenia appear "valid" from a prognostic but not from a familial perspective (23). This puzzling result is explicable if the factors that influence the outcome of a psychiatric syndrome are not closely related to those which influence its familial transmission. For example, the pattern of psychopathology in relatives may not differ for probands with *DSM-III* schizophrenia and schizophreniform disorder, two disorders that, by design, differ substantially in prognosis (24). The different "validators" proposed for psychiatric disorders may not all provide the same answer. Such results will make the job of psychiatric nosologists more complex, requiring an evaluation of the relative importance of different potential validators for psychiatric syndromes.

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Resilient Adolescents Whose Parents Have Serious Affective and Other Psychiatric Disorders: Importance of Self-Understanding and Relationships

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Eighteen young men and women whose parents had major affective disorders, often in combination with other serious psychiatric disorders, were selected from a larger sample on the basis of their good behavioral functioning as adolescents at initial assessment. When they were reassessed an average of 2½ years later, 15 of the 18 were still functioning well. Considerable self-understanding, a deep commitment to relationships, and the ability to think and act separately from their parents characterized these young people. Many of them were taking care of their ill parents. The implications of these findings for preventive and clinical intervention are discussed.

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Although extensive empirical research has documented serious psychopathology in the children of parents with affective illness (1–6), no studies have appeared on youngsters in this risk group who are adapting well. Such study forms a necessary complement to the description of psychopathology (7). The best predictors of later functioning are often indices of adaptation rather than psychopathology (8, 9). Moreover, knowledge about what is protective—what characterizes young people at risk who are functioning well—should provide a basis for the development of both clinical intervention and prevention programs for youngsters whose parents have affective disorders.

There has been considerable interest in studying the adaptation of children and adolescents in various other high-risk situations, resulting in longitudinal studies of youngsters at risk because of diminished economic resources, minority status, or other factors (8, 10, 11), epidemiological studies (11), studies of response to particular stressful circumstances such as medical illness (12), and studies of the children of schizophrenic parents (13), including some studies of successful adaptation (14). Several findings from these studies guided the design of our investigation. Researchers have agreed that the description of the subjects' current behavioral functioning is the essential first step in describing adaptation and resiliency (7). This approach has the advantage of being reliable and objective, since ratings are made on actual behavior or reported behavior rather than inferred processes. Second, relationships have been found to be protective in a wide variety of risk situations (10, 15–17). Because parental affective illness seriously impairs relationships within the family (18–20), the possible protective effects of relationships are relevant to the study of resilient offspring of parents with affective disorders. Finally, investigators have recognized the importance of other protective factors in resilient youngsters. These include constitutional factors, for example, certain temperamental characteristics (21). Also important are ways of responding, thinking, and acting, for example, certain coping styles (12, 22), positive self-esteem, and a sense of being in control (23).

Within this broad domain, previous work of the first author (24–26) demonstrated that self-understanding was an essential component of resilient individuals who dealt successfully with various stressful situations; thus, it was a focus of the current study. Self-understanding is of interest because it is potentially amenable to intervention. The reflections of young people who have seriously affectively ill parents give a clear sense of exactly what experiences are troublesome and difficult for them. Also, given the lack of standardized and validated measures of resiliency, investigation of a subject's own perceptions of what enabled him or her to function effectively provides important information for understanding the psychological processes involved in such adaptive behavior.

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METHOD

A group of resilient adolescents was selected by objective criteria from a larger sample of child and adolescent subjects who had been part of a previous study of the impact of parental affective illness. This small group was reinterviewed 1½–3 years after the initial interview to assess the stability of their adaptive functioning, to characterize their adaptive behavior, and to allow them to describe their experiences with ill parents and their understanding of themselves. It was hypothesized that young people who were adapting well to parental affective illness had developed and would manifest considerable self-understanding.

Sample Selection in the Larger Study

Inclusion in the larger study required that the families be Caucasian and English speaking, that they have children 6–19 years old who lived with their mothers, and that there be data available on both biological parents.

Subjects were drawn from three main sampling groups: parent subjects recruited from a large study of the course and outcome of serious affective illness (27), subjects recruited through a door-to-door survey of neighborhoods in which families with clinically identified affective illness lived, and a random sample of subjects from a prepaid health plan. We used this sampling design in order to assess whether the impact of affective illness identified by community survey or random sampling was similar to that for parent subjects being treated in clinical centers. This proved to be the case. Previous analyses (6) had shown that combining these sampling groups into a single pool of subjects was in general a reasonable approach.

Initial Interview Assessments

A standard structured research interview, the Schedule of Affective Disorders and Schizophrenia (SADS) (28), scored according to the Research Diagnostic Criteria (RDC) (29), was used to characterize parental lifetime psychopathology (1, 6). Lifetime psychopathology in the children was assessed according to *DSM-III* criteria by a consensus rating on standardized interviews with the youngsters (Diagnostic Interview for Children and Adolescents [30, 31]) and with the mothers about their youngsters on the parent version of the same diagnostic interview. The adaptive functioning of the youngsters was assessed by means of the Garmezy Child Interview (32) and, from the mother's perspective about the child, by means of the Rochester Adaptive Behavior Inventory (33, 34).

Parents were interviewed separately from their offspring by an interviewer blind to any knowledge of the findings on the children. Only biological parents were assessed because the overall study design called for the exploration of family patterns of inheritance. All mothers were interviewed; both biological parents were interviewed whenever possible, and when this was not possible, information on the fathers was obtained from the mothers. This occurred in the majority of the cases.

Each subject was assigned an overall rating of adaptive functioning (6, and summary scale for the Rochester Adaptive Behavior Inventory [L. Wynne, personal communication]) for the 3 months before interview on the basis of all information collected from the child and from the parent about the child. Ratings were made on a 9-point scale (1=above-average functioning, 9=seriously disturbed). The overall rating of adaptive functioning was based primarily on specific ratings of discrete areas of behavioral functioning, i.e., school performance, work performance, involvement in other activities, and relationships with mother, father, siblings, and friends. In meetings between the interviewers and a senior psychiatrist, consensus ratings for diagnoses and adaptive functioning were made from the reports of the parents and children according to specified criteria for resolving discrepancies between the accounts.

The main findings of the larger study—much higher rates of general psychopathology and of major depression as well as lower overall adaptive functioning in the youngsters at risk than in those not at risk—have been previously described (1, 2), as has the relative weight of various parental risk factors in relation to youngsters' outcomes (6).

Selection of Sample of Resilient Young People

Subjects with good overall ratings of behavioral functioning (adaptive function scores of 1–3) at initial assessment and without major current psychiatric disorder were considered for the follow-up study if they met the following inclusion criteria: 1) they were at least 12 years old at the time of initial assessment, 2) they were at least 6 years of age at the time of some parental affective illness, 3) they were living with the ill parent at the time of parental illness, and 4) there was a history of serious parental affective illness. These criteria were used to ensure that the subjects had experienced the parental affective illness when they were old enough to remember it and that they themselves were old enough to reflect about their experiences. Clinical review of the cases was also conducted to ensure that the youngsters had been exposed to serious disorder and had been functioning well at initial assessment. From a large number of families with serious affective disorders who had children over age 12, 19 families providing 23 subjects met all the requirements. Three potential subjects were excluded from the follow-up study because they would have been markedly older than the rest of the sample at follow-up. All the remaining subjects were recontacted, and 18 (90%) from 14 families agreed to be reexamined. Informed consent was obtained from all subjects in the study.

Subsequent Interview

Two separate domains, behavioral functioning and self-understanding, were examined at reinterview. The major areas of previously studied behavioral adaptive functioning during the 3 months before interview were systematically reassessed by a shortened version of the initial research interview with the youngsters themselves. The major important diagnoses identified in the adolescents in the previous study—affective disorder, substance abuse, and conduct disorder—were reassessed with a shortened version of the Diagnostic Interview for Children and Adolescents (30, 31) for the interval since first assessment.

On the basis of previous work (24–26), we developed an interview that addressed systematic questions to the subjects about their awareness, experience, and understanding of their parents' illness. They were directly asked what they believed had enabled them to deal with the illness, what aspects were most difficult for them, and what advice they would give to others. Most of the subjects were seen in their own homes for several hours, and in all cases they were interviewed by the same research associate (D.P.) who had interviewed them initially.

The interviews were summarized by the interviewer, and these summaries were reviewed separately by the interviewer and by the senior researcher (W.R.B.) to determine the main content areas. Behavioral functioning was summarized for each individual by using the scales developed in the initial study (overall adaptive functioning and specific 5-point scales, ranging from 1=outstanding to 5=poor, that measured relationships with peers, friends, mother, and father and functioning in school, at work, and in other activities). Three components of self-understanding were identified and examined in the 18 summaries: awareness of the parent's illness, specific response to parental illness, and capacity to observe and reflect on the experience of parental illness and other matters.

FINDINGS

The mean age of the parents at initial assessment was 43 years (range=34–53 years). The most common lifetime RDC diagnosis was major depressive disorder (12 cases), followed by alcoholism (10 cases) and intermittent depression (eight cases). Seventeen of the 28 parents had experienced affective illness, sometimes in combination with nonaffective disorder; four had never been ill; and seven had experienced nonaffective illness only. The presence of only nonaffective diagnoses for some parents is explained by the fact that some individuals with affective illness had spouses with a nonaffective illness. Most of the illnesses were chronic; for example, the mean duration of a child's lifetime exposure to parental affective disorder was 4.5 years (range=8 weeks to 15 years, median exposure=4.4 years). In 10 of the 14 families, both parents were ill. The rate of divorce or separation was 64% (nine of 14 families).

The young men and women ranged in age from 13 years to 19 years and 10 months at the time of the first assessment. They were reassessed an average of 30 months after the first assessment, when they ranged in age from 14 years and 6 months to 22 years and 8 months; the mean age was 19. There were eight young men and 10 young women.

No history of serious medical problems in this group was elicited at either assessment. The overall IQ of the subjects was well above average: the lowest full-scale IQ was 92 and the highest was 137, with a mean of 113.5. There were no instances of diagnosable learning disorders in this group. At initial assessment, four youngsters had met criteria for a *DSM-III* disorder at some time during their lives.

Quantitative Findings: Follow-Up Assessment

Fifteen of the 18 individuals had overall adaptive functioning scores that represented good functioning (between 1 and 3 on the 9-point scale) at both assessments, whereas three individuals had scores above 3 at the time of the second assessment. Examination of the component ratings that contributed to the overall score showed consistently high scores for the 15 with good ratings.

In terms of *DSM-III* diagnoses in the interval between the first and second assessments, no subjects had developed conduct or substance abuse disorders, but three subjects had had depressive disorders; two of them were episodes of major depression and one was a dysthymic disorder. One of these occurred in a young woman who had had a previous episode of depression.

Of the 18 young men and women, 16 described themselves as valuing close, confiding relationships and emphasized that these relationships were a central part of their lives. These relationships were with a wide variety of individuals (11 subjects were extremely close to their mothers, four to their fathers, 11 to siblings, and 13 to friends).

Thirteen subjects were attending school. Most of these were extensively and deeply involved in their academic pursuits, and several were attending or planned to attend prestigious colleges. In addition to academic work, they reported deep involvement in and commitment to their jobs. Of the seven in college, all had part-time and summer jobs, and of the six in high school, three had part-time jobs. Of the remaining five, four had at least one full-time job and three held two jobs. They manifested the ability to persist in their work; all but one had good work and academic histories. The one young person with a poor school and work history had such a history only for the recent past.

Furthermore, all but two of the 18 subjects reported having intensive and varied activities outside of work and school and took pleasure in these outside activities. Several were deeply involved in athletics, particularly those who were still in school.

Description of the Experience of Parental Affective Illness

All of the young men and women were deeply aware of their parents' illness. They described their experience of parental illness in terms of changes in parental behavior or outlook. Observable changes in parents included irritability, sadness, lack of energy, and for some, excessive drinking. Many of the respondents reported the loneliness and isolation of their parents' lives. Several commented that their parents tried not to show their distress and attempted to keep their depression to themselves.

The young people's accounts focused on the disruption of their own lives that was associated with or was a consequence of parental illness, rather than on the identification of the parents' behavior as the sequelae of depression. This disruption included economic hardship and change of house or apartment, as well as lack of parental awareness and involvement.

The young people described in detail major life events associated with their parents' illness and often related the parental illness to the presence of painful life events. Especially important were parental divorce, deaths in the family, and for a few, serious medical illnesses of the parents.

The young people described their experiences as full of disillusionment, confusion, and feelings of helplessness. Many described the loss of a role model or an idealized loved one. An important theme in their accounts was the sick parent's unavailability to perform usual tasks, as well as their own considerable initial anger and frustration about not knowing what was going on. Nine individuals specifically mentioned turning to an identified other person during episodes of severe parental illness in order to make sense of the experience or to derive comfort.

More generally, relationships were crucial for many of these young people in allowing them to separate from their parents, whether this was during an acute illness episode of the parent or not. Two subjects reported turning to an adult outside the family in this process, and two turned to a sibling perceived as a best friend. Four individuals felt the need to flee the family and found that close friends provided a refuge and base away from the family despair so that they were able to continue their own lives.

Eleven young men and women assumed a caretaking role either within the family or outside it. This included taking charge of all the family functions, managing finances and living situations, caring for younger children, and calling attention to the parent's illness, which in some cases led to assistance and recovery. They served as peacemakers, supported younger siblings, and cheered up depressed mothers. Two other young women, although they were not involved in a major caretaking role within their families, were pursuing careers in the helping professions. Three others were the siblings of those who were caretakers and thus might not be expected to assume that role.

Understanding of the Parents' Illness and Subjects' Relation to It

Understanding of themselves and their parents' illness was evident in many ways in the 15 individuals who were coping well. First, they were able to reflect on changes over time in themselves and in their parents' behavior. They were able to talk about their concerns when they first became aware of their parents' illness and about the ways in which they came to see both themselves and their parents' situation differently over time.

Second, they were able to distinguish clearly between themselves (and their own experiences) and their parents' illness. Thus, they were able to talk about their parents' difficulties and, in many cases, be saddened by them and empathic and yet not be overwhelmed. For example, they did not expect that their own life experiences in the future would be the same as those of their parents. Third, they were clearly able to think and to act separately from their parents' illness system. Finally, before the interview, they had reflected on their relationships and their experiences with their parents. They had somehow made peace with or come to an understanding of the experience, and this was important to them; the interview tapped into this ongoing process of understanding.

In all cases, the young people who functioned well had noticed that there was something wrong with their parents and had concluded that they were not the cause of their parents' illness. They claimed that the realization that they were not the cause was crucial to understanding what was happening and to their capacity to deal with the experience of having a sick parent. This understanding of what was happening in the life of the parent and that they were not to blame was markedly absent in the three young people who were not functioning well at the second assessment. These three had not separated from their parents; they felt left out and angry or saw themselves as the ill parent's lifeline. The parents of these three subjects had not discussed their depression with them. Two of these young people had themselves experienced depression in the interval since the first assessment.

DISCUSSION

Behaviorally defined good adaptation was relatively stable in these individuals, since 15 of the 18 subjects had high ratings at the two assessment times. This was the first study, to our knowledge, to examine the stability of the adaptive functioning of resilient young people in this risk group, and the finding of such stability points to the value of a behaviorally rated adaptive function measure in identifying resilient individuals. Furthermore, it is the first study to report the considerable extent of such young people's awareness of their parents' affective illness and their reflections on their experiences.

The young men and women who adapted well were doers and problem solvers. Their accounts reflected a deep pride and sense of efficaciousness in their actions. This is the opposite of the helplessness and hopelessness so often described as accompanying depression (35). Several subjects commented that it was this problem-solving, action orientation—a rejection of extraneous thoughts—which enabled them to function so well.

Taken together, these accounts reflect the association of good adaptive functioning with self-understanding. This was not a prospective study and so self-understanding cannot yet be described as a protective factor for the individuals in the sample. With that qualification, however, the accounts of these individuals allow for a definition of the components of self-understanding in those who were functioning well.

1. Accurate cognitive appraisal of the stress to be dealt with. The importance of adequate cognitive appraisal has been emphasized by a number of researchers in stress and coping (12, 36), primarily in response to medical illness or immediate situational stresses. In the present study cognitive appraisal involved an awareness of various aspects of parental illness over a period of time and changes in the awareness as the parent's illness changed.

2. Realistic assessment of one's capacity to act and realistic expectations of the consequences of the action. These young men and women were able to delineate what they were and were not responsible for in relation to their parents' illness system. As an example, many of them had wished to save or change their parents and had tried to do so, but over time they had come to accept the fact that they could not cure their parents, although they could in certain important ways contribute to their well-being. Moreover, their assessments were accurate in the sense that they did not see themselves as responsible for the illness. Self-reflection was an important part of this process.

3. Actions that reflect understanding or are congruent with it. These individuals described themselves as separate from their parents' illness system and not responsible for it. They acted without depending on their parents, seeking independent relationships and functioning independently at work and in school.

The use of objective criteria to define the sample and the recruitment of 90% of the available subjects who met the criteria increase the generalizability of the findings, since these subjects were representative of resilient young people in the various sampling groups we studied. The use of the in-depth life history method in combination with structured assessments of psychopathology and behavioral functioning allowed a fuller and more detailed understanding of the subjects' experiences with their sick parents than either method alone would have provided. An important life dimension for many of them was the caretaking role that they assumed in relation to the parent who was ill. Interestingly, although they were separate and able to function independently, they remained very involved with their ill parents. For example, all of those who attended college did so in the metropolitan area in which their families lived rather than going to other cities. All remained connected to at least one parent.

These subjects were selected because they had had a period of good functioning in the 3 months before the first interview. They were selected without reference to prognosis or history of past difficulties, and the time interval between the two assessments was relatively short. They are now entering the age that is at highest risk for the onset of affective disorders and are at risk in the future because of both genetic factors and their psychosocial exposure to chronic impairments in parental functioning (37).

These youngsters faced and were affected by multiple serious stresses, not simply episodes of pure affective illness in a parent. These included divorce or separation in the majority of cases, illness of both parents in the majority of cases, and nonaffective psychiatric disorders, especially alcoholism, in the parents. Given the nature of the sample, it is likely that these multiple stresses in combination are encountered by the majority of youngsters growing up in homes where there are serious parental affective disorders.

The ratings and descriptions of the processes of self-understanding were made by the two investigators in the project and were based on clear definitions of the concepts for specific content areas in the interview. Such an approach was necessary because of the large amount of interview material involving reflections at different points in time. In the future, specific quantitative ratings of dimensions of self-understanding applicable to clinical and research endeavors need to be developed.

A prospective study of the development of self-understanding, the various stages in its unfolding, and its role as a protective factor against future difficulties would provide different and needed information. Clearly, self-understanding of these young people evolved over time. They were at a point in their development (late adolescence and early adulthood) when an appropriate developmental task is separating from parents, and this requires self-reflection. It is likely that both the role and the nature of self-understanding are different at other points in development.

This was not a study of the etiology of the young people's resiliency. Clearly they had certain constitutional factors, such as above-average intelligence, lack of serious medical illness, and lack of neurodevelopmental disabilities, that contributed to their adaptation and may well have contributed to their capacity to understand themselves. Furthermore, they clearly manifested a variety of important psychological qualities and ego strengths, including courage, motivation, and a strong sense of personal integrity. The method of inquiry and focus on self-understanding provides a useful way of obtaining information about and characterizing these dimensions, yet they are clearly distinct from self-understanding.

Both the role of self-understanding and the role of caretaking in other samples of subjects in this risk situation and in other risk situations, especially parental alcoholism, deserve much fuller study.

These individuals were deeply aware of and deeply affected by their parents' illness. The actual stresses that they faced varied, for example, psychiatric illness in the mother or the father, divorce, and physical disease in a parent. Clinicians working with youngsters who have parents with serious affective illnesses should carefully inquire about the presence and meaning of individual experiences as they try to help these young people make sense of what has occurred. In this study, what bothered the subjects was often associated with, but different from, the parent's affective illness itself and was different for different subjects.

Depression and other affective illness in parents are public health problems of major proportions. Fully 20% of women and 8%–12% of men will experience an episode of major depressive disorder during their lifetimes (38). The number of youngsters growing up in families exposed to these conditions is considerable; thus, there is a need for preventive strategies (39). One preventive approach that grows naturally from our work is to develop strategies for all youngsters in this risk situation for enhancing separateness from the parent's illness system, strong intimate relationships, and self-understanding which characterized the resilient young men and women in this study.

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Pedigrees, Functioning, and Psychopathology in Families of School Phobic Children

Gail A. Bernstein, M.D., and Barry D. Garfinkel, M.D., F.R.C.P.(C)

Family pedigrees of six children with severe school phobia compared with those of a matched group of families of five children with psychiatric disorders showed a clustering of affective and anxiety disorders. Blind and independent family histories and structured interviews of parents and siblings demonstrated higher rates of depressive and anxiety disorders in first-degree relatives of children with school phobia. Parents of children with school phobia described more disturbance in family functioning on the Family Assessment Measure than did parents in the comparison group in the areas of role performance, communication, affective expression, and control.

(Am J Psychiatry 1988; 145:70–74)

Adult anxiety disorders, specifically agoraphobia (1) and panic disorder (1–3), show a strong familial pattern. Similarly, childhood and adult depression have been found to cluster in families (4, 5). Additionally, a familial relationship between anxiety disorders and major depressive disorders has been identified. Adult patients with major depressive disorder plus anxiety disorder have a higher familial risk of both major depression and anxiety disorders than patients with major depression alone (6).

Patients with chronic, severe school phobia often meet *DSM-III* criteria for both depressive and anxiety disorders (7). To our knowledge, there have been no systematic family studies with school phobic children as probands.

Clinical reports of the families of individuals with school phobia have emphasized various disturbances in family interactions, especially a poorly resolved dependency relationship between the mother and the child with school phobia, who has trouble separating from the mother (8, 9). Mothers of children with school phobia have been depicted as overprotective, controlling, and ambivalent; their children receive contradictory messages regarding independence (10, 11). This study was designed to examine the pedigrees of families with a school phobic child and to assess different aspects of functioning in these families.

We hypothesized that children with school phobia who met diagnostic criteria for both depressive and anxiety disorders would have first-degree relatives with a higher prevalence of depressive and anxiety disorders than would the relatives of a matched group of psychiatric patients.

METHOD

Six patients were selected from 42 children and adolescents evaluated in the School Phobia Outpatient Clinic in the Division of Child and Adolescent Psychiatry at the University of Minnesota. Patients selected had the highest scores on anxiety and depression scales as tested at initial evaluation. The mean±SD score for the six patients on the Children's Depression Rating Scale (12) was 54±9.36; on the Children's Manifest Anxiety Scale (13) it was 16.5±4.85. Patients ranged in age from 7 years, 7 months, to 18 years, 2 months (mean age=12 years, 10 months). There were four boys and two girls.

The patients selected were demographically representative of the group of 42 patients from which they were selected. All six were Caucasian, and all came from middle and lower socioeconomic classes (Hollingshead III, IV, and V). Three were in single-parent families, four had at least a 2-year history of symptoms, and four had failed to respond to previous treatment.

Five of the six children with school phobia met criteria on structured interview for an affective disorder: three had a major depressive episode and two had an adjustment disorder with depressed mood. All six patients met criteria for anxiety disorder: one had separation anxiety disorder, four met criteria for both separation anxiety disorder and overanxious disorder, and one had only overanxious disorder.

Five of the six children with school phobia were matched on sex, age, and socioeconomic status with another child or adolescent evaluated in the Child and

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Adolescent Psychiatry Outpatient Clinic. Comparison patients included four boys (three had attention deficit disorder and one had attention deficit disorder and simple phobia) and one girl (she had bulimia and conduct disorder). Informed consent was obtained from all probands, control subjects, and their families.

The following instruments were administered to the six children with school phobia, the five children with other disorders, and their parents and siblings.

1. The Family History Research Diagnostic Criteria (FH-RDC) instrument (14) uses a semistructured interview to obtain psychiatric diagnostic information about family members in addition to or instead of direct interview. Diagnoses made from the FH-RDC include affective disorders, schizophrenia, substance use disorders, and antisocial personality disorder. For this study, additional questions were asked to cover anxiety and eating disorders; *DSM-III* criteria were used for these questions.
2. The Diagnostic Interview for Children and Adolescents (15) was completed for each patient and sibling from 10 to 18 years of age, and the Diagnostic Interview for Parents of Children and Adolescents (15) was completed for each patient and sibling between 5 and 10 years of age. These instruments cover major *DSM-III* child and adolescent disorders.
3. The National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS) (16) was completed for each parent. The DIS covers lifetime *DSM-III* adult diagnoses.
4. The parents completed the MMPI (17), the Beck Depression Inventory (18), and the Sheehan Patient-Rated Anxiety Scale (19). The first part of the Sheehan scale covers recent symptoms of anxiety and the second part covers current symptoms of anxiety.
5. The general scale of the Family Assessment Measure, third revision (20), was used to assess family relationships and interactions. An overall score, seven clinical subscale scores, and two response style subscale scores (social desirability and defensiveness) were obtained.

Three independent interviewers who were blind to the status of the children as index or comparison group members and to the study's hypothesis obtained interview information and conducted tests according to the following protocol.

1. One interviewer obtained the FH-RDC data from the child's parents, often both parents, regarding the child's first- and second-degree relatives.
2. A second interviewer administered the DIS, MMPI, Beck inventory, Sheehan scale, and Family Assessment Measure to each patient.
3. A third interviewer administered the Diagnostic Interview for Children and Adolescents and the Family Assessment Measure to each proband and sibling. Probands or siblings between 5 and 10 years of age were not interviewed; instead, a parent was interviewed about the child with the Diagnostic Interview for Parents of Children and Adolescents. Children 5 years old or younger were not studied.

TABLE 1. Diagnoses of Anxiety and Depressive Disorders[a] in First-Degree Relatives of Six Children With School Phobia and Five Matched Children With Psychiatric Disorders

	Parents		Siblings[b]	
Diagnosis	Of Children With School Phobia (N=12)	Of Control Children (N=10)	Of Children With School Phobia (N=10)	Of Control Children (N=5)
Anxiety disorder only	3	3	4	0
Depressive disorder only	2	0	2	0
Both anxiety and depressive disorders	4	0	1	0
Total anxiety and/or depressive disorder	9	3	7	0

[a] Diagnoses were obtained from Family History Research Diagnostic Criteria (FH-RDC) and confirmed by using the Diagnostic Interview Schedule (DIS) for parents and the Diagnostic Interview for Children and Adolescents (DICA) or the Diagnostic Interview for Parents of Children and Adolescents (DICA-P) for siblings; DIS, DICA, or DICA-P diagnoses took precedence over FH-RDC diagnoses.

[b] Only siblings older than 5 years were studied.

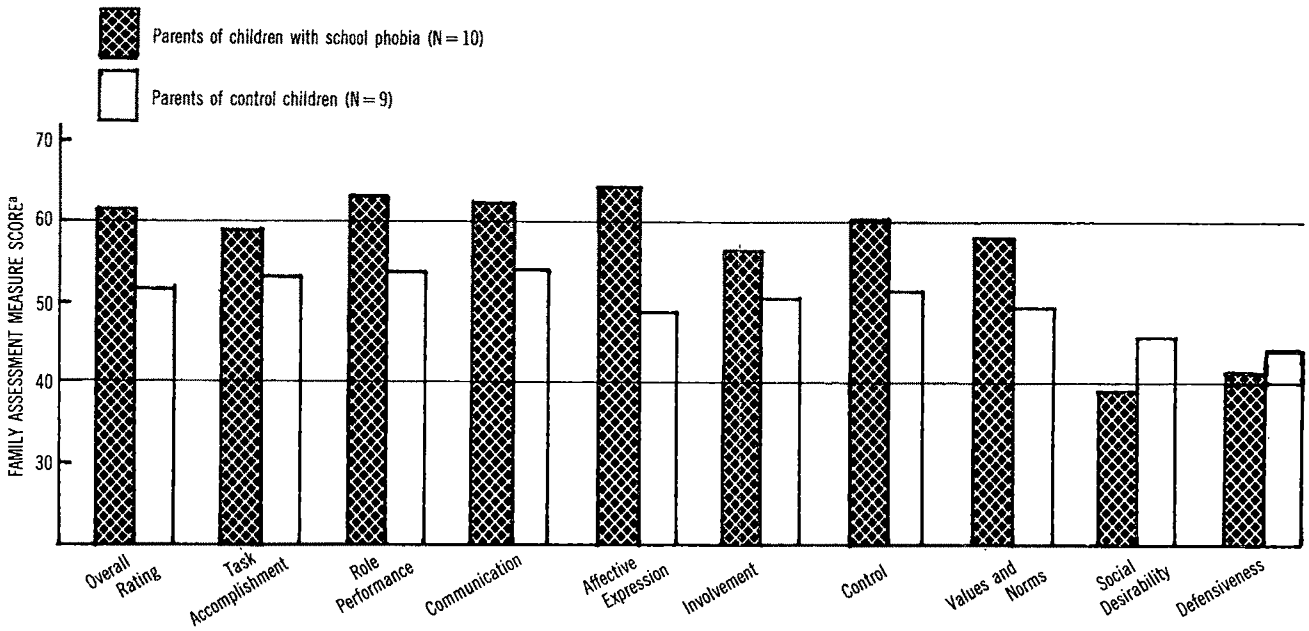
RESULTS

In four of the six families of children with school phobia, anxiety and depressive disorders were present in both maternal and paternal family members and in three generations of relatives. For the children with school phobia, 82 first- and second-degree relatives were evaluated; for the control children, 57 first- and second-degree relatives were evaluated. Fourteen (17%) of the 82 first- and second-degree relatives of children with school phobia had anxiety disorders alone, 10 (12%) had depressive disorders alone, and 10 (12%) had both anxiety and depressive disorders; among the 57 relatives of control children, however, nine (16%) had anxiety disorders only, two (4%) had depressive disorders alone, and three (5%) had both.

Twelve parents of children with school phobia and 10 parents of the control children were evaluated. As table 1 shows, most of the parents of the school phobic children but only three of the control children's parents met criteria for either anxiety or depressive disorders. Of the seven parents of school phobic children who met criteria for anxiety disorders, two had agoraphobia with panic attacks, one had agoraphobia, three had generalized anxiety disorder, and one had social phobia. The three parents in comparison families with anxiety disorders included one with panic disorder, one with generalized anxiety disorder, and one with social phobia.

Many parents met criteria for alcohol and/or drug use disorders. Six of the nine parents of children with school phobia who had depressive and/or anxiety disorders also had alcoholism or drug use disorder, compared with only one parent in the comparison group (drug abuse without affective or anxiety disorder).

FIGURE 1. Scores on the Family Assessment Measure of Parents of Six Children With School Phobia and Parents of Five Matched Children With Psychiatric Disorders



^a Scores above 60 indicate family dysfunction; scores between 60 and 40 are in the average range; scores below 40 indicate family strength.

Ten siblings of school phobic children and five siblings of control children were evaluated. All siblings were older than 5. Table 1 shows that most of the siblings of school phobic children but none of the siblings of control children had anxiety and/or depressive disorders. Of the five siblings of school phobic children who met criteria for anxiety disorders, one had separation anxiety disorder and four had simple phobia.

Using Student's t tests (two-tailed), we found no significant difference between parents of school phobic children and parents of comparison children on the Beck inventory ($t=1.69$, $df=17$), part 1 of the Sheehan scale ($t=1.29$, $df=16$), and part 2 of the Sheehan scale ($t=0.58$, $df=17$). The low Beck inventory and Sheehan scale scores suggest that parents receiving a lifetime diagnosis of depression and/or anxiety disorder on the DIS were in remission when interviewed.

On the Family Assessment Measure (20), parents of children with school phobia reported family dysfunction at a clinically significant level; their mean standard score was over 60 on the overall scale (average of seven subscales) and on the subscales of role performance, communication, affective expression, and control (figure 1). Student's t tests (two-tailed) indicated that parents of school phobic children described significantly poorer role performance ($t=2.40$, $df=17$, $p<0.03$), affective expression ($t=2.80$, $df=17$, $p<0.02$), and overall rating ($t=2.27$, $df=17$, $p<0.04$) than parents of control children. To correct for the large number of Family Assessment Measure variables, the Bonferroni inequality (21) was also used to calculate statistical significance (e.g., when N variables are studied, 0.05/N is the level needed for significance). With this more conservative approach to the data, only one subscale (affective expression) differentiated the two groups. Parents of school phobic children scored low on defensiveness and social desirability.

The MMPI mean profiles of parents of school phobic children showed no clinical abnormalities (T scores >70). Although the mean profiles of mothers and fathers of school phobic children had no clinical scale scores over 70, the individual profiles of three of the five mothers and one of the five fathers had elevated clinical scale scores. These profiles were suggestive of persons with passive-aggressive character traits (elevation on psychopathic deviate and paranoia scales), except for one mother who had the profile of an anxious-depressed individual.

DISCUSSION

The strengths of this investigation include the use of blind, independent observers and the use of a matched psychiatric group for comparison purposes. In addition, diagnoses made by FH-RDC were confirmed by direct structured interviews, thus increasing diagnostic certainty. To our knowledge, this is the first systematic, blind, controlled family interview study of parents and siblings of children with anxiety disorders.

Although there are several advantages in this study, there are also shortcomings. Limitations include the small sample size, leading to possible type II errors (missing important differences), and the large number of variables, leading to possible type I errors (falsely declaring that group differences exist when none really does). In addition, probands meeting criteria for two disorders (anxiety and depressive disorders) were evaluated. This combination of disorders has been the most common presentation in the patients seen in our school phobia clinic (7). Children with both disorders are the most severely symptomatic, as indicated by higher scores on anxiety and depression scales (7). The pedigrees of the children with the most severe school phobia were studied to identify familial disorders, if they exist. However, the results may be skewed in the direction of a higher occurrence of psychopathology in relatives of school phobic probands than might be found with less severely affected individuals. The mixed diagnoses in the comparison group further complicate the results.

The pedigrees of school phobic children show higher risk for affective and anxiety disorders. These data on children parallel the findings of Leckman et al. (22) with adults. Their study showed that first-degree relatives of adult probands with both major depression and panic disorder have higher rates of major depression, anxiety disorders (phobias, panic disorder, and generalized anxiety disorder), and alcoholism than interrelatives of normal subjects or of depressed probands without anxiety disorders. This pattern was also demonstrated in their children. Depression in the parent increased the risk of depression in the children. Depression plus anxiety disorder, especially panic or agoraphobia, in a parent added additional risk for depression and anxiety disorder in offspring (23). Panic disorder in parents resulted in a threefold greater risk for separation anxiety in the children (23).

The findings of our study and those of Leckman et al. (22) and Weissman et al. (23) suggest a close interrelationship between major depression and anxiety disorders. It has been suggested that panic disorder and major depression in adults have a common underlying diathesis (22). Similarly, perhaps in children there is a common predisposition to severe separation anxiety and major depression. An alternative explanation is that severe anxiety disorders and major depression may be two distinct conditions that share many characteristics resulting in frequent diagnostic errors.

Children with school phobia can be divided into four subgroups: those with both affective and anxiety disorders, those with affective disorder only, those with anxiety disorder only, and those with no affective or anxiety disorder (7). In this study, five of the six children with school phobia met criteria for both depressive and anxiety disorders. Future studies will look at the pedigrees of the remaining subgroups of school phobic children to allow comparison. Livingston et al. (24) found no difference between the family histories of children with severe anxiety disorders and those of children with major depression. Both family histories demonstrated a high rate of affective disorders and alcoholism.

The parents of children with school phobia viewed their families as more dysfunctional than did the parents of control children in the areas of role performance, communication, affective expression, and control. An elevation of the role performance scale score indicates a lack of clarity regarding roles, resulting in conflict. An endorsement of the items on the communication subscale suggests ambiguous messages and a lack of understanding among family members. Elevation of the affective expression score indicates inhibition of painful affect, which may lead to tensions and to overreactions.

An elevated control subscale score suggests that a family is unable to adapt its usual patterns of functioning to cope with changing demands due to rigidity. Often the school phobic child assumes a pivotal, controlling role in the family by refusing to go to school, thus creating power struggles between parents and child.

The family members of school phobic children were interviewed an average of 12 months after the child's initial evaluation, during the summer, when children with school phobia have fewer symptoms, and after the children had received treatment in the school phobia clinic. Therefore, it was expected that the family members would be experiencing improved family functioning. Conversely, comparison families were assessed shortly after the child's initial evaluation, at a time of probable increased stress and family crisis. These factors would be expected to maximize family difficulties in the comparison families and minimize difficulties in index families. With our reverse findings, the importance of the dysfunction in the families of school phobic children must be emphasized.

In the current study, the group mean MMPI profiles of the parents of the school phobic children did not show significantly higher clinical scale scores, although 70% of these parents were diagnosed as having a lifetime diagnosis of a depressive and/or anxiety disorder. Perhaps the episodic nature of affective and anxiety disorders and the possibility that the parents were tested during a period of remission explain the normal findings. This is supported by the observation that the parents' scores on the Beck inventory and Sheehan scale were low at the time of interview. Another possible explanation is that the questions on the MMPI are not well correlated with *DSM-III* criteria for anxiety or the FH-RDC for depression.

Findings from this study suggest that there is a higher rate of depressive and anxiety disorders in first-degree relatives of school phobic patients with severe symptoms. Thus, children with severe school phobia who have both depression and anxiety may have a specific familial pattern that replicates their clinical presentation. This is consistent with the family study of Leckman et al. (6), which showed that depression plus anxiety disorder has different familial patterns than depression alone. To help confirm the family patterns observed in this study, further family pedigree studies will use school phobic probands with anxiety disorders alone and depressive disorders alone as well as children without either diagnosis who are having trouble attending school.

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Relationship of Chronic Pelvic Pain to Psychiatric Diagnoses and Childhood Sexual Abuse

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Structured psychiatric and sexual abuse interviews were administered to 25 women with chronic pelvic pain and a comparison group of 30 women with specific gynecological conditions. All 55 patients underwent diagnostic laparoscopy, and the results of the fiberoptic pelvic examination were objectively classified by the study gynecologist, who was blind to the psychiatric diagnoses. The patients with chronic pelvic pain showed a significantly higher prevalence of major depression, substance abuse, adult sexual dysfunction, somatization, and history of childhood and adult sexual abuse than the comparison group. There were no significant differences between the groups in severity or type of pelvic pathology.

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The evaluation and treatment of chronic pelvic pain in women have been both a clinical challenge and a source of controversy. Chronic pelvic pain accounts for 5%–10% of all laparoscopies performed (1), at a cost of approximately $1,500 per procedure. There are no accurate statistics for the frequency of laparoscopies done in the United States to evaluate chronic pelvic pain, but in 1978 in Great Britain alone, more than 10,000 diagnostic laparoscopies were performed to evaluate lower abdominal pain (2). Despite the increasing frequency of laparoscopic investigation, there is little consensus in the literature that organic factors are of primary etiological importance in chronic pelvic pain; reported prevalence rates of pelvic pathology range from 8% to 83% (1, 3, 4).

Since the pioneering article by Duncan and Taylor in 1952 (5), there has been much debate about the relative contributions of psychological and biological factors to this condition. The majority of investigators have suggested that psychological factors are primary (1, 5–19), while a small number of studies point to organic causes (3, 20). A third group argues that psychological disturbance is a precipitant for the psychophysiologic development of pelvic congestion (5, 6). Childhood sexual abuse and adult sexual adjustment problems have been repeatedly reported in patients with chronic pelvic pain (5, 7, 10, 13, 15), and these patients have been described as neurotic, anxious, and depressed, with chaotic family backgrounds (8–10).

Many of the studies, however, suffer from serious methodological flaws (21): 1) lack of structured psychiatric interviews and operational criteria for diagnosis, 2) lack of appropriate control groups, 3) lack of a valid measure of the degree and nature of organic pathology, 4) assumption of cause-effect relationships between pathology and pain, 5) biased sampling (sampling from populations with known psychopathology), and 6) small sample size.

The present study attempted to correct these methodological deficiencies and to add to existing knowledge about the relationship between organic and psychological determinants of chronic pelvic pain.

METHOD

The subjects were 25 women with a history of chronic pelvic pain which was of at least 3 months' duration. The cases were sequentially taken from the laparoscopy surgery schedules of a university hospital, a county hospital, and two urban private practices. In addition, a comparison group of 30 women who were being evaluated for infertility problems (N=17) or bilateral tubal ligation (N=13) were selected in the same manner. All of the 55 women studied underwent diagnostic laparoscopy. The findings from the procedures were rated by the study gynecologist (L.R.H.) according to the American Fertility Society Classification for Endometriosis (22). This classification rates pelvic pathology (adhesions and/or endometriosis) found in the tubes, ovaries, peritoneum, and cul-de-sac on a scale of 0 to >40 points. There are four stages of pathology based on the following scores: 1–5=stage I (minimal pathology), 6–15=stage II (mild pathology), 16–40=stage III (moderate pathology), and >40=stage IV (severe pathology).

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The women were also interviewed by one of two interviewers (L.H., J.H.-G.) using the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (23). The psychiatric and gynecological raters were blind to each other's findings. In addition, a detailed family history was obtained by using the Family History Research Diagnostic Criteria (24), and a sexual abuse history was taken by means of a structured interview developed for a large epidemiologic study of sexual abuse in the general population (25). Finally, the SCL-90 (26) was administered to all patients.

The interviewers were trained by the senior study psychiatrist (W.K.), who had used the DIS in many previous studies. Ten percent of the interviews were independently scored by a psychiatrist, with 100% agreement between that psychiatrist and the interviewers regarding the patients' diagnoses. Eighty-three percent of the women with chronic pelvic pain and 73% of the comparison group whom we approached agreed to participate in this study and signed consent forms.

Chi-square tests with Yates' correction were used to examine the relationship between patient groups and all discrete measures such as psychiatric diagnoses, somatic symptoms, and history of sexual abuse. Two-tailed t tests were used to determine whether pelvic pain patients differed from the comparison group in age, education, occupational status, number of somatic symptoms, and psychological test scores.

The subjects were divided into four groups for comparison: 1) chronic pelvic pain patients with laparoscopic pathology scores greater than 0 (at least minimal pathology was found), 2) chronic pelvic pain patients with pathology scores of 0, 3) comparison group members with pathology scores greater than 0, and 4) comparison group members with pathology scores of 0.

RESULTS

No significant differences were found between the group of women with chronic pelvic pain who had positive laparoscopy findings and those with chronic pelvic pain who had negative laparoscopy findings in psychiatric diagnoses, history of sexual assault or abuse, scores on the SCL-90, or family history of psychiatric illness. Similarly, no significant differences were found in any of these categories between the comparison group with positive laparoscopy findings and those with negative laparoscopy results. Therefore, the patients with chronic pelvic pain (N=25) were compared with the gynecological comparison group (N=30).

The 25 pelvic pain patients and the 30 women in the comparison group did not differ with respect to the amount of pathology found by laparoscopy techniques; 12 (48.0%) of the patients with chronic pelvic pain had no pathology, and 14 (46.7%) in the comparison group had no pathology. There also was no significant difference in the severity of pathology; chronic pelvic pain patients in whom pathology was found by laparoscopy scored a mean±SD of 4.0±6.4 (corresponding to stage I, minimal pathology) on the American Fertility Society classification, and the women in the comparison group had a mean±SD pathology score of 3.8±6.0. The type of pathology was also quite similar in both groups; adhesions were the most common finding. To determine whether these results could be attributed to the severity of pathology, we divided the groups according to severity and compared subjects within the pelvic pain group and within the comparison group on all of the variables of interest (childhood sexual abuse, psychiatric diagnoses, SCL-90 scores). The pathology groups did not differ on any variable within the group of women with chronic pelvic pain or within the comparison group. Thus, keeping in mind the limits of the data analysis and the small sample sizes, we do not believe that the results of the study were due to differing amounts of pathology between the two groups.

The patients with chronic pelvic pain had a median duration of pain of 24 months (range=3–85 months). The women with chronic pelvic pain were significantly younger (mean±SD age=27.0±5.9 versus 31.9±4.9 years; t=3.38, df=53, p<0.001), were less likely to be married (36% versus 80%; χ^2=9.24, df=1, p<0.002), and had a significantly lower occupational status (Hollingshead score: mean±SD=7.5±3.6 versus 4.4±2.9; t=3.53, df=53, p<0.001) but did not differ in their educational status (Hollingshead score: mean±SD=3.1±1.1 versus 2.4±1.2; t=1.61, df=53, n.s.).

Psychiatric Diagnoses

The women with chronic pelvic pain had a significantly greater prevalence of lifetime major depressive illness and current major depressive illness than the women in the comparison group (see table 1). The 16 patients with chronic pelvic pain who had had episodes of depression during their lives had a median of 4.2 episodes per patient; moreover, for 12 of these 16 patients, the first episode of major depression occurred before the onset of chronic pelvic pain.

Although only one pelvic pain patient and none of the women in the comparison group was diagnosed as having somatization disorder, the women with chronic pelvic pain had a significantly greater mean±SD number of positive somatic symptoms (7.2±4.8 versus 1.7±1.9; t=5.88, df=53, p<0.001) on the somatization disorder section of the DIS than the patients in the comparison group. Significantly more patients with chronic pelvic pain suffered from the 11 symptoms listed in table 2. As can be seen, many of these are not gynecological symptoms and reflect the tendency of the patients with chronic pelvic pain to amplify and suffer from multiple somatic symptoms.

Significantly more women with chronic pelvic pain reported a history of drug abuse or dependence than did comparison group subjects (see table 1). Nine of

TABLE 1. Psychiatric Diagnoses of 25 Women With Chronic Pelvic Pain and 30 Women With Specific Gynecological Conditions

Diagnostic Interview Schedule Diagnosis	Pelvic Pain Patients N	Pelvic Pain Patients %	Comparison Subjects N	Comparison Subjects %	χ^2 (df=1)	p
Depression, lifetime	16	64	5	17	11.02	<0.001
Depression, current	7	28	1	3	4.84	<0.05
Somatization disorder	1	4	0	0	—	n.s.
Phobias, current	8	32	3	10	4.12	<0.05
Panic disorder, current	2	8	0	0	—	n.s.
Alcohol dependence or abuse, lifetime	9	36	7	23	—	n.s.
Alcohol dependence or abuse, current	5	20	6	20	—	n.s.
Drug dependence or abuse, lifetime	13	52	6	20	6.16	<0.01
Drug dependence or abuse, current	3	12	1	3	—	n.s.
Functional dyspareunia	13	52	2	7	11.94	<0.001
Inhibited orgasm	4	16	1	3	0.22	<0.05
Inhibited sexual desire	7	28	2	7	4.53	<0.05
Inhibited sexual excitement	7	28	5	17	—	n.s.

TABLE 2. Somatic Symptoms of 25 Women With Chronic Pelvic Pain and 30 Women With Specific Gynecological Conditions

Symptom	Pelvic Pain Patients N	Pelvic Pain Patients %	Comparison Subjects N	Comparison Subjects %	χ^2 (df=1)	p
Abdominal pain other than pelvic	13	52	3	10	11.66	<0.001
Dysmenorrhea	15	60	6	20	9.24	<0.05
Nausea	8	32	1	3	8.19	<0.01
Gas/bloating	11	44	4	13	6.43	<0.05
Difficulty in walking	5	20	0	0	6.60	<0.05
Shortness of breath	6	24	1	3	5.25	<0.05
Dizziness	7	28	2	7	4.53	<0.05
Weakness	9	36	1	3	9.78	<0.01
Being sickly during entire life	7	28	1	3	6.68	<0.01
Irregular menstrual periods	8	32	0	0	11.23	<0.001
More than two missed periods	8	32	2	7	5.88	<0.05

the 13 patients with a history of drug abuse had abused drugs before the onset of their chronic pelvic pain; the median age at onset of pain was 17.1 years.

A significantly greater number of the pelvic pain patients than of the patients in the comparison group had a *DSM-III* diagnosis of adult sexual dysfunction (see table 1), including functional dyspareunia and inhibited sexual desire. For inhibited orgasm, although the chi-square value was nonsignificant because of the relatively small number with that diagnosis, the actual association was significant (phi coefficient=−0.22, $p<0.05$).

There were no significant differences between the chronic pelvic patients and the comparison patients in the percentage who had at least one family member with depression (32% versus 30%), alcohol abuse (44% versus 46%), or drug abuse (20% versus 10%). However, the families of chronic pelvic pain patients had a significantly higher mean±SD total (2.2±2.0) of first-degree family members with a depression spectrum diagnosis (depression, alcohol abuse, or drug abuse) than did the families of the comparison patients (1.3±1.1) ($t=2.15$, df=53, $p<0.05$).

The patients with chronic pelvic pain had significantly higher mean scores on all SCL-90 scales except the interpersonal sensitivity scale than the comparison group patients did (see table 3).

History of Sexual Abuse

Sixty-four percent of the women with chronic pelvic pain had experienced some type of sexual abuse at or before the age of 14, compared to 23% of the women in the comparison group, a statistically significant difference (see table 4). The pelvic pain patients also had suffered a significantly greater prevalence of sexual abuse as adults than had the comparison patients. Only the women who had been victims of severe sexual abuse as children had chronic pelvic pain.

Women who had had any experience of sexual abuse as children were significantly more likely to have one of the four adult sexual psychiatric problems screened by the DIS. Thus, 74% (N=17) of the women who had been sexually abused as children suffered from an adult sexual dysfunction, compared to 34% (N=11) of the women who had not been sexually abused as children ($\chi^2=6.86$, df=1, $p<0.01$)

The women who had been sexually abused as children also had significantly higher lifetime risks of major depression (56% versus 25%; $\chi^2=4.33$, df=1, $p<0.05$) and drug abuse (57% versus 22%; $\chi^2=5.53$, df=1, $p<0.05$) than the women who had never been sexually abused. Moreover, all four women who had suffered severe childhood sexual abuse had had one or more major depressive episodes in their lifetimes as well as a diagnosis of drug abuse sometime during their lives (all four of the women had chronic pelvic pain).

We divided the patients according to whether or not they had experienced childhood sexual abuse and examined the relationship between lifetime depression and pelvic pain. For women who were not victims of

TABLE 3. SCL-90 Scale Scores of 25 Women With Chronic Pelvic Pain and 30 Women With Specific Gynecological Conditions

	Score of Pelvic Pain Patients		Score of Comparison Subjects			
SCL-90 Scale[a]	Mean	SD	Mean	SD	t (df=48)	p
Hostility	58.3	12.0	46.7	12.3	3.34	<0.01
Phobic anxiety	50.1	17.2	36.9	12.8	3.12	<0.01
Paranoia	53.4	14.6	43.8	14.8	2.28	<0.05
Psychoticism	61.4	15.2	43.3	14.2	4.33	<0.001
Somatization	60.6	12.5	49.6	9.0	3.58	<0.001
Obsessive-compulsive	58.0	14.1	46.2	11.5	3.24	<0.01
Interpersonal sensitivity	57.2	15.6	53.1	11.0	—	n.s.
Depression	63.2	10.1	51.7	9.1	4.20	<0.001
Anxiety	62.0	11.5	45.0	11.7	5.10	<0.001
Global symptom index	62.0	11.3	49.3	8.2	4.61	<0.001
Positive symptom total	61.3	12.2	50.5	8.2	3.74	<0.001

[a] SCL-90 scales were converted to standardized (t score) norms for psychiatric patient populations.

TABLE 4. History of Sexual Abuse of 25 Women With Chronic Pelvic Pain and 30 Women With Specific Gynecological Conditions

	Pelvic Pain Patients		Comparison Subjects			
Item	N	%	N	%	χ^2 (df=1)	p
Sexual abuse as a child (age 14 or younger)	16	64	7	23	7.67	<0.01
None	9	36	23	77		
Mild[a]	12	48	7	23		
Severe[b]	4	16	0	0		
Sexual abuse as an adult (after age 14)	12	48	4	13	6.35	<0.01
None	13	52	26	87		
Mild[a]	5	20	1	3		
Severe[b]	7	28	3	10		

[a] Exhibitionism, fondling, aborted attempts at sexual assault.
[b] Rape by a family member or other person.

abuse, there was no relationship between pelvic pain and lifetime depression (χ^2=1.29, df=1, n.s.). However, for women who had been sexually abused, there was a statistically significant relationship (χ^2=5.04, df=1, $p<0.05$). All but one of the women who had been sexually abused as children and had a history of depression developed pelvic pain.

DISCUSSION

A highly significant difference was found in the prevalence of childhood sexual abuse and adult sexual abuse between the chronic pelvic pain patients and the comparison patients. The rate of childhood sexual abuse for the control subjects (23%) was similar to the rate (32%) found in the study, mentioned previously, of 930 women in the general population that used the structured sexual abuse questionnaire (25), whereas the rate of childhood sexual abuse in patients with chronic pelvic pain (64%) was double the rate found in the general population survey. The patients with chronic pelvic pain also had significantly higher rates of adult sexual problems (dyspareunia, inhibited orgasm, and inhibited sexual desire) than the control subjects, and there was a highly significant correlation between being a victim of sexual abuse as a child and having a problem with adult sexual dysfunction. Our data demonstrating high rates of childhood sexual abuse and adult sexual dysfunction in patients with chronic pelvic pain support the findings of past studies (5, 7, 10, 13, 15).

The patients with chronic pelvic pain also had a significantly higher prevalence of histories of major depression (64% versus 16%) and of a current major depressive episode (28% versus 3%). In addition, the chronic pelvic pain patients with a history of depression had a median of four episodes, and three-quarters of these patients had had a depressive episode before the onset of pelvic pain. Several studies have found that medical patients with major depression had significantly higher rates of medical care utilization than nondepressed control subjects (27, 28). In addition, they had significantly more medical complaints on a review of systems (29, 30) and frequently made nonspecific complaints to their physicians—psychophysiological complaints as well as pain complaints (28). Also, studies of patients with a wide variety of chronic pain complaints (headache, backache, chest pain, abdominal pain) have demonstrated high rates of depressive illness (31–35). Moreover, our present study finding that affective illness usually preceded the chronic pelvic pain is consistent with reports that affective illness often precedes chronic back pain and chest pain (32, 33). The results of both the present study and past studies suggest that chronic pelvic pain in many patients is strongly associated with a lifetime history of depression and that the location of the pain is chosen because of childhood sexual traumatization and the resulting adult sexual problems. In fact, the association between depression and chronic pelvic pain was significant only in women who had been sexually abused as children.

Somatization was also significantly more common in the women with chronic pelvic pain (an average of 7.0 positive somatic symptoms on the DIS somatization section) than in the control group (an average of 1.7

symptoms). Few of these women met the *DSM-III* criteria for somatization disorder, but as several studies (36–38) have reported, there is a large group of women in primary care clinic populations who have chronic somatic symptoms yet fall short of the criteria for somatization disorder. These women tend to have gynecological complaints, backaches, and headaches. The studies have also described a strong association between these women with chronic somatic complaints and a family history as well as a personal history of alcohol abuse. The present study did find a significantly higher prevalence of first-degree family members with depression spectrum disorders, a trend toward a higher rate of personal history of alcohol abuse, and a significantly higher rate of lifetime drug abuse (56% versus 20%) for patients with chronic pelvic pain than for comparison subjects. The patients with chronic pelvic pain had a median age at onset of drug abuse of 17 years, and nine of the 13 patients with a history of drug abuse began to abuse drugs before the onset of chronic pelvic pain.

There was no significant difference between the patients with chronic pelvic pain and the control patients in the prevalence of organic pathology or in the severity of pathology, despite the fact that one group had pain and the other did not. A serious flaw in many previous studies was the assumption that there was a cause-effect relationship between pathology and pain. Thus, if pathology was discovered on laparoscopy, it was assumed that the lesion was the cause of the pain. Despite the usefulness of laparoscopy in helping to make reports of pelvic pathology more objective, there is still no way to determine the adequacy of a pathological stimulus to produce pain, since it is a subjective experience of multideterminate cause. The fact that the same percentage of patients with pelvic pain and of comparison patients was found to have organic pathology, and that there was no difference in the type or degree of pathology, suggests that for most women with pelvic pain the pathological findings have little or no relevance to the chronic pelvic pain, which is due primarily to the past and present psychological problems of the patient. In addition, the organic pathology in some women does cause a nociceptive input of painful stimuli, but the nociceptive stimulus is often amplified by the patient's psychological problems. One caution here is that the number of patients in this study was relatively small, and our results need to be replicated in larger samples. Also, it is likely that in some women (probably the minority), the nociceptive input is the primary problem, and either there are no associated psychological problems or the psychological problems are secondary to the chronic pain.

A hypothesis which can be drawn from the data we have presented is that many patients with chronic pelvic pain come from multiproblem families in which they are not adequately protected, and thus they become victims of childhood sexual abuse, often by relatives or friends of the family. As a result of the lack of care and protection and the childhood sexual abuse, women with chronic pelvic pain are likely to have adult sexual problems, including decreased desire for intimacy, dyspareunia, and problems with orgasmic function. They often have problems with recurrent depressive episodes and drug abuse, most likely also as sequelae to the early lack of care and protection. In a recent study that supports this hypothesis (39), Gold found that women with a history of childhood sexual victimization were significantly more likely to have a poor adult sexual adjustment, had more depressive symptoms and lower self-esteem, and suffered from a greater number and intensity of psychological symptoms according to the SCL-90.

Chronic pelvic pain may be a metaphorical way of describing chronic psychological pain and may act as a defense or coping mechanism to protect against painful, emotion-laden memories. Moreover, the symptoms of pelvic pain have social efficacy: the pain often leads to avoidance of adult sexual contact due to dyspareunia. Thus, as postulated by Gidro-Frank et al. (9), pelvic pain may result from intrapsychic conflicts about sexuality and intimacy that lie repressed until the beginning of regular sexual activity, at which time pelvic pain develops so that sexual activity and intimacy—and the severe anxieties and painful memories associated with this activity—are avoided.

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Rectifying an Archaic Payment Policy

For more than 20 years, major medical and technological advances have become available to the elderly through expansion of benefits under the Medicare program. Yet outpatient mental health benefits—despite the great strides made in the treatment of mental illness since the inception of Medicare—have been unchanged. An archaic payment policy reflecting real discrimination against mental illness and its treatment has severely restricted access to needed care. The elderly receive annually only $250 for every $500 expended on outpatient mental health services regardless of the severity of their problems or the types of services they should receive.

Why have mental illness treatment benefits lagged so far behind new treatment technology? The answer is that Congress has been and continues to be concerned about the fiscal implications of unlimited coverage. Certainly today, with control of the nation's budget deficit a major priority, some way of managing costs and building in cost-effectiveness measures must be developed if even modest benefit improvement is to occur.

Although I have been concerned about limited access to appropriate mental health services for many years, that interest crystallized as a result of my participation in a recent legislative symposium sponsored by the American Psychiatric Association. I pledged my support for efforts to obtain a responsible expansion of the outpatient mental health services benefit and asked my staff to explore development of a bill to do so. I sought expert advice and developed a proposal based, in part, on information presented in two articles by Goldman, Taube, and associates, which are included in this issue of the *Journal*.

The data and analysis offered in "High Users of Outpatient Mental Health Services," parts I and II, fit with our intent—to expand coverage for beneficiaries most in need of care and to provide improved access for those with mental health problems. First, the data suggested that acute medical care for chronic psychiatric conditions is delivered in a manner virtually identical to the outpatient management of severe and chronic somatic disorders. I believe that the public is ready to pay for care of patients with mental disorders who receive treatment similar to that provided for other medical conditions and disorders.

Second, the analysis demonstrated that only 10% of users make more than 24 visits per year. But this group of "high users" accounts for 50% of outpatient mental health expenditures. I became convinced that a "visit limit" designed to control costs could be constructed on the basis of these data.

Last, the reports indicated that 50% of users make no more than two mental health visits per year. I concluded that this information would be useful in creating a strategy to reduce access barriers to early intervention for those who make only a few mental health visits. Would improved access aid the elderly facing severe personal crises due to death of a spouse or close friend, loss of a job, failing health, change of residence, or economic difficulties?

As I traveled around Minnesota, I became more and more convinced that the answer was yes and that we must make this change.

In this instance, as is often the case, a potential solution to a longstanding public policy problem could be devised only after the conclusion of sound technical analysis and credible research. I believe the public will continue to support such research, and

I congratulate the *Journal* for its foresight in publishing research results of such relevance to public policy.

I am also convinced that our $512 billion national investment in health care can buy us a lot more health—both physical and mental health. By making payment and policy coverage decisions on the basis of well-done research, we can have a more effective and efficient health system. I am also confident that legislative efforts stimulated by quality public policy research will result in the achievement of better access to mental health services.

DAVE DURENBERGER

The author is a U.S. Senator from Minnesota. Address reprint requests to Senator Durenberger, U.S. Senate, Washington, DC 20510.

De Anno Mirabile

The observant reader with a penchant for the study of journal mastheads will have noticed a number of recent major changes in the *Journal's* editorial staff.

First and foremost, after 22 years as Managing Editor of *The American Journal of Psychiatry,* Mrs. Evelyn S. Myers retired from her post on July 1, 1987. The first to hold that position, which was created by Dr. Francis J. Braceland on his assumption of the duties of Editor in 1965, she served with grace and distinction. The cherished colleague of two Editors during her long tenure, she played a central role in bringing the *Journal* to prominence as a scientific publication and provided the vital thread of continuity that allowed the *Journal* to function without losing a stitch despite the many changes in Staff that occurred over more than two decades. In addition to her significant contributions to the *Journal* itself, Mrs. Myers earned an international reputation for her work and ideas through activities in other professional arenas, such as the Council of Biology Editors (CBE); she was for a time Editor of that organization's publication, *CBE Views.* On Thursday, the 25th of June, some 250 friends and admirers gathered in the Francis J. Braceland Modern Founders Room of APA's Washington Headquarters at a farewell reception in her honor. In the closing words of a sonnet read during that celebration in tribute to Mrs. Myers' unique contribution to the *Journal,*

> Of her who stays behind in all our hearts
> One cannot say in truth that she departs.

We all wish her well, with deep affection, as she turns now to new interests and accomplishments on the Staff of APA's Office of Economic Affairs.

On July 6, 1987, we welcomed Ms. Melanie Miller as the new Managing Editor of the *Journal.* Ms. Miller comes to us from St. Louis after completing a 5-year term as Managing Editor of *Circulation.* The heart must truly be the seat of the soul, for Ms. Miller has made the transition from cardiology to psychiatry with great aplomb, sensitivity, and finesse. The *Journal* is indeed fortunate to have her.

It is a pleasure, as well, to note the appointment of Drs. John J. Bartko and Lee Gurel as Statistical Editors. Their titles are an appropriate recognition of their part in initiating and implementing a new program of statistical review, which will be the subject of an editorial in a forthcoming issue of the *Journal.* Their contribution is a significant step toward strengthening the *Journal's* review of manuscripts, and we are indebted to them and to the following individuals who have agreed to serve as statistical referees.

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And last but by no means least, we must acknowledge the many men and women who have acted as reviewers during the past 12 months. A selfless band of mute but dedicated scholars, they have worked tirelessly week in, week out, and we break at least the anonymity of their silent labors to express our gratitude for what they have contributed to our collective scientific life as referees of *Journal* manuscripts during the period from November 1, 1986, to October 31, 1987.

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The Editor is particularly indebted to his fellow members of the Editorial Board. Dr. Morris A. Lipton, the Deputy Editor, and Dr. Nancy C. Andreasen, our Book Forum Editor, have performed with distinction during the year, and the Associate Editors have similarly given unstintingly of their time and counsel. It was, furthermore, a great pleasure to welcome Dr. Kenneth L. Davis to the Editorial Board as an Associate Editor, filling the position made vacant when Dr. Andreasen completed the second of her 4-year terms of office.

Special recognition should be accorded Ms. Linda Loy, who, as Assistant Managing Editor, has played a vital role in keeping the *Journal* going during a year of major changes in editorial personnel. The Editor is deeply grateful to her and the rest of the Staff for so effectively bridging the period of transition.

No matter how busy his schedule, our Medical Director, Dr. Melvin Sabshin, always has time for the *Journal*'s affairs. The Editor is ever appreciative of his friendship and advice, as well as the continuous support of the Board of Trustees.

Our particular gratitude is also extended to Drs. Robert J. Campbell III, Donald W. Hammersley, William A. More, Harold A. Pincus, Carolyn B. Robinowitz, Jeanne Spurlock, John A. Talbott, and Jack W. White; to Mses. Laura Abedi, Kathleen Bryan, Teddye Clayton, Carol Davis, Nancy Frey, Lisette Gibson, Zing Jung, Karen Loper, and Beth Prester; and to Messrs. John Blamphin, Richard Cermak, Herbert M. Gant, Steve Jones, Joel Klein, Ronald McMillen, and Raymond J. Purkis, Jr.

And so, as we come to the end of the *Journal*'s *annus mirabilis*—this truly extraordinary year for us of change and innovation—the Editors and Staff wish our readers, friends, and colleagues a happy and productive 1988.

J.C.N.

Growth Hormone-Releasing Factor Stimulation Test in Depression

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The authors administered the growth hormone-releasing factor (GRF) stimulation test to 19 patients with major depression and 19 age- and sex-matched control subjects to test the hypothesis that a blunted growth hormone (GH) response to clonidine reflects a central α_2-adrenergic receptor subsensitivity in depression. GH response to GRF was significantly higher in patients with depression than in control subjects. This group difference was mainly attributable to three of the 19 depressed patients who exhibited markedly high GH responses to GRF. These results suggest that the blunted GH response to clonidine seen in patients with depression is not due to a pituitary defect in GH secretion.

(Am J Psychiatry 1988; 145:90–92)

Several investigators have demonstrated that clonidine-induced growth hormone (GH) secretion is clearly lower in depressed patients than in normal control subjects (1–3), leading to the hypothesis that there is a central α_2-adrenergic receptor subsensitivity in depression (3). However, this hypothesis is based on the assumption that the pituitary somatotroph response to growth hormone-releasing factor (GRF) is not lower than normal in depression.

When administered to normal individuals, GRF produces a robust increase in GH secretion (4). Lower doses of this peptide (0.1, 0.33, and 1 μg/kg of body weight) have produced a monophasic GH response with no side effects (4). Thus, given the safety and availability of GRF and the importance of determining whether there is a defect in the somatotroph response to GRF, we performed the GRF stimulation test in depressed patients and age- and sex-matched control subjects. The dose we used, 1 μg/kg of body weight, was based on earlier dose-response studies (4). Because body weight appeared to be an important variable in somatotroph sensitivity to GRF, we attempted to match patients and normal volunteers for body weight.

METHOD

We studied 19 patients (11 men and eight women) who met Research Diagnostic Criteria (RDC) (5) for major depression, endogenous subtype, and 19 age- and sex-matched control subjects after obtaining informed consent. All patients were evaluated by the attending psychiatrist and a research psychiatrist (K.R.R.K. or K.R.). All clinical information, including information derived from a semistructured interview, the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (6), was used in arriving at the diagnosis. The interrater reliability (kappa) for the two psychiatrists for the diagnosis of RDC major depression, endogenous subtype, was 1, on the basis of five interviews. Patients about whom there was any doubt regarding the diagnosis were not admitted into the study. All patients admitted into the study were with-

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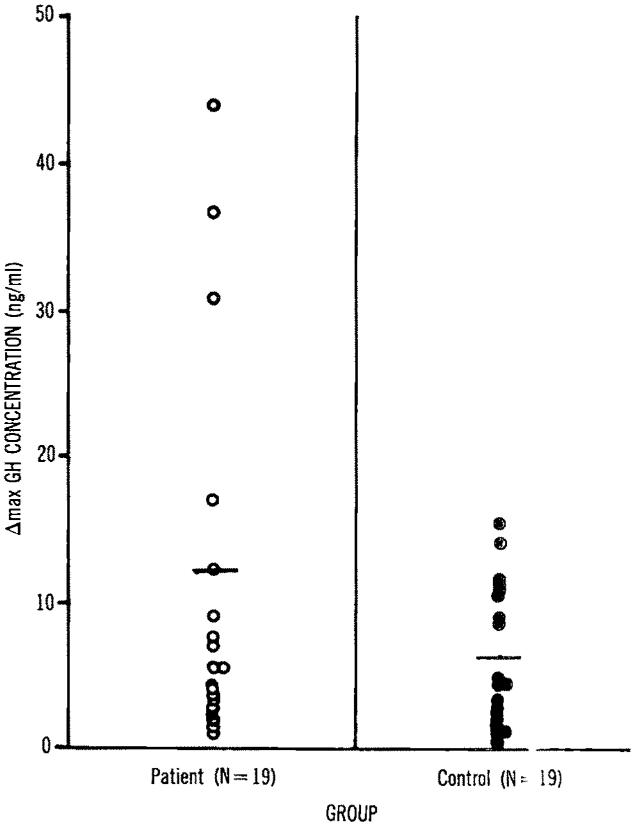
out substantial medical illness as assessed by a complete physical examination, laboratory evaluation, and thyroid function tests. Premenopausal women were studied within the first week after cessation of menstruation. All patients were drug-free for at least 1 week before testing. Normal healthy volunteers were individually age- and sex-matched to the patients and had no history of psychiatric disorders. No morbidly obese patients were included in the study.

Synthetic human pancreatic GRF was prepared for administration as follows. The peptide was dissolved in sterile 0.001 N HCl, 0.001 N ascorbic acid (USP), 154 nM NaCl, and 0.9% (weight by volume) benzyl alcohol containing 10% (weight by volume) mannitol (USP) and 0.25% human serum albumin (USP) at a concentration of 1 mg/ml and sterilized by filtration. Aliquots of 200 μl (200 μg) were then placed in 5-ml glass vials, sealed, frozen, and kept at –56°C until used (4). The GRF stimulation test was conducted as follows: subjects remained recumbent throughout the study and fasted from midnight until the test was completed. A catheter was placed in a forearm vein between 7:30 and 8:00 a.m.; blood was collected at 15-minute intervals through the catheter for GH measurement. GRF was administered as an intravenous bolus of 1 μg/kg at 9:00 a.m. Over the next 3 hours, blood was collected in heparinized Vacutainers for GH assay at –15, 0, 15, 30, 45, 60, 90, 120, and 180 minutes after administration of GRF, and the samples were immediately placed in ice. The blood was centrifuged within 15 minutes at 4°C, and the plasma was stored at –80°C until assay. Human GH was measured by a specific, solid phase, double monoclonal antibody assay (Hybritech). Inter- and intra-assay coefficients of variation were 15.0% and 6.7%, respectively. All results are given as mean±SD values. Samples from each patient and the matched control subject were analyzed in the same assay. The data were analyzed with the Wilcoxon matched-pairs signed-rank test (from which a z score was derived), Student's t test, and Spearman's rank correlation coefficient.

RESULTS

There was no difference in age between patients (39.3±14 years) and control subjects (39.4±15 years). There was no significant difference in body weight between patients (70.57±15.20 kg) and control subjects (75.63±13.97 kg). Further, basal GH levels were not significantly different between patients (0.75±0.13 ng/ml) and control subjects (0.66±0.24 ng/ml). The peak GH concentrations were significantly higher in patients (12.80±13.00 ng/ml) than in control subjects (7.34±5.30 ng/ml) ($z=2.17$, $N=19$, $p<0.025$, and $t=2.13$, $df=18$, $p=0.045$). As shown in figure 1, the maximum change (Δ_{max}) in GH concentrations after GRF was also higher in patients (12.06 ± 13.30 ng/ml) than control subjects (6.68 ± 5.20 ng/ml) ($z=-1.97$, $N=19$, $p<0.05$, and $t=2.05$, $df=18$, $p=0.056$). In 14 of the 19 matched pairs, the Δ_{max} GH in the patient exceeded that in the control subject. There was no difference in the time of peak concentration between patients (48.9±32.0 minutes) and control subjects (48.2±35.2 minutes).

FIGURE 1. GH Response to GRF in 19 Depressed Patients and Matched Control Subjects



The sex of the patient did not correlate with the GH response to GRF. There was a significant negative correlation between age and peak GH response ($r_s=-0.38$, $N=38$, $p=0.02$). In addition, there was a strong negative correlation between body weight and peak GH response ($r_s=-0.54$, $N=38$, $p=0.001$).

Two subjects, one patient and one control subject, had basal GH concentrations more than 3 ng/ml (but less than 5 ng/ml). Exclusion of these two subjects and their matched subjects did not change the results. The differences in maximum GH concentration and GH response to GRF between patients and control subjects were almost totally accounted for by three patients who demonstrated markedly high GH responses to GRF. No differences between patients and control subjects were found when the three patients and their matched control subjects were excluded. One of these three patients had psychotic depression. Three of the remaining 16 patients also satisfied criteria for psychotic depression. In 14 of the 19 pairs, the patient had a GH response higher than the control subject. Three of the four patients with psychotic depression had a higher GH response to GRF than their matched control subjects. The number of subjects in the study was too small to relate GH response to specific clinical features.

Of the 19 patients, 15 were taking no psychotropic medication for at least 2 weeks before the study, and 13 of these patients were free of psychotropic medications for at least 1 month before the study. There was no difference in GH response to GRF between patients who were taking medications 1 week before the study and those who were not taking any psychotropic medications for 2 weeks or more. Only one of the three patients with a markedly exaggerated GH response to GRF had been taking any medications; this patient was taking doxepin 1 month before the study.

DISCUSSION

Our results reveal a high degree of variability in GH response to human pancreatic GRF. The response observed in the depressed patients was significantly greater than in normal control subjects. This study suggests that the blunted GH responses to clonidine (1–3) and provocative stimuli such as *d*-amphetamine (7) seen in depressed patients are probably due to a suprapituitary defect. The fact that GH secretion stimulated by hypoglycemia and *d*-amphetamine is blocked by α_2-adrenergic antagonists (8) and the finding that clonidine-induced GH secretion is blunted in depression strongly suggest that the blunted GH secretion to provocative stimuli in depression is due to a defect at central α_2-adrenergic receptors, probably in the hypothalamus (3). Further support for this possibility is provided by the finding of Corn et al. (9) that the GH response to apomorphine was normal in a cohort of depressed patients who had a significantly blunted GH response to clonidine.

The exaggerated GH response to GRF seen in some depressed patients might be a reflection of reduced secretion of hypothalamic somatostatin, which functions as a GH-inhibiting factor. This would be consistent with reports of low somatostatin concentrations in the CSF of depressed patients (10, 11). Further studies measuring CSF somatostatin on the day of administration of GRF in depressed patients and normal volunteers may be important in determining the cause of the exaggerated GH response to GRF seen in our depressed patients.

Our results also confirm prior observations that both age and weight are important factors in the GH response to GRF (4, 12). Although a previous study on GH response to GRF emphasized the importance of weight as a factor in morbidly obese individuals, our results suggest that weight is a critical variable even in those who are not morbidly obese (12). Future studies of GH response to GRF must strictly control for weight and age.

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Response of Psychotic and Nonpsychotic Depression to Phenelzine

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The authors studied 52 depressed inpatients to examine treatment response to phenelzine, a monoamine oxidase (MAO) inhibitor. All patients were classified into one of three RDC categories (definitely psychotic, probably psychotic, and nonpsychotic). For the entire sample, the mean platelet MAO inhibition level achieved with phenelzine was greater than 80%. Response to treatment was determined by independent clinical assessment and by the change in rating scores from baseline; 68% of the nonpsychotic, 43% of the probably psychotic, and 21% of the definitely psychotic patients were classified as responders. This differential response rate is similar to that reported in the literature for tricyclic antidepressants.

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Despite recent interest in MAO inhibitors (1), we are unaware of a study specifically addressing a differential response rate to phenelzine with respect to the treatment of psychotic and nonpsychotic depressions. The literature (2–6) indicates that 65%–70% of nonpsychotically depressed patients but only 25%–30% of psychotically depressed patients respond to a tricyclic antidepressant alone. We attempted to clarify whether such a differential response rate to phenelzine exists in a heterogeneous group of depressed inpatients classified as having a nonpsychotic, probably psychotic, or definitely psychotic depression.

METHOD

Informed consent was obtained after the study had been fully explained to 52 inpatients (33 women and 19 men) who fulfilled Research Diagnostic Criteria (RDC) and *DSM-III* criteria for various depressive disorders (43 with major depression; four with bipolar disorder, depressed; one with schizoaffective disorder, depressed; and four with minor depression). The mean±SD age of the sample was 47.8±15.7 years. All participants underwent a drug-free washout period (mean±SD=15±7 days) before initiation of treatment and received a tyramine-free diet throughout their hospitalization. At the end of the washout phase, platelet MAO activity levels and clinical ratings were obtained and repeated weekly during the treatment phase. Platelet MAO activity was determined with a modification of the radiometric method of Squires (7), as described by Pandey et al. (8).

Clinical rating scales included the Hamilton Rating Scale for Depression or the Affective Disorders Rating Scale (unpublished scale prepared by McDonald-Scott et al.) as well as the Global Assessment Scale (GAS) and the Zung Self-Rating Depression Scale. All ratings were done by clinicians experienced with the battery of instruments and blind to MAO levels. Overall severity of depression was calculated by assigning 2 points for the definite presence of three RDC subtypes (endogenicity, recurrence, and incapacitation), 1 point for probable presence, and 0 points for absence (i.e., range=0–6). In addition, 0, 1, or 2 points were assigned for the total baseline Hamilton scale scores (i.e., 2=≥30; 1=27–29; 0=<27). Classification into response, partial response, and nonresponse categories was determined by three independent clinicians' evaluations of the patients' overall improvement during treatment. This determination was then correlated with changes in the Hamilton scale ratings: responders manifested at least a 40% drop (i.e., final Hamilton scale group mean±SD score=9.6±5.1); partial responders did not achieve a 40% reduction but did show consistent improvement across all ratings (i.e., final Hamilton scale group mean±SD score=18.6±3.6); and nonresponders did not show more than a 30% drop in their Hamilton scale scores or achieve an absolute final score of less than 21 (i.e., final Hamilton scale group mean±SD score=31.0±6.5). Patients were rated as definitely psychotic, probably psychotic, or nonpsychotic on the basis of RDC criteria for the presence or absence of delusions and/or hallucinations.

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Patients were given phenelzine at an initial dose of 15 (N=36) or 30 (N=16) mg b.i.d., and after 2 weeks the dose was adjusted on the basis of clinical response. Phenelzine was eventually increased to a maximum dose of 90 mg/day if adequate clinical response was not achieved at a lower dose and the patient could tolerate the side effects (mainly sedation and/or orthostatic hypotension).

Analysis of the data included 1) the nonparametric Mann-Whitney U test for the effect of psychosis on response, 2) a logit model (9, 10) to test for trends in proportions (i.e., does the proportion of nonresponders increase linearly with increasing levels of psychosis?), and 3) a multiple variable probit analysis (11) to adjust for the effects of a series of moderator variables (endogenicity, recurrence, incapacitation, sex, initial dose, age, overall severity rating, and baseline Hamilton scale score) on the relationship between psychosis and response.

RESULTS

At the end of treatment, we observed that 21 (68%) of 31 nonpsychotic patients, three (43%) of seven probably psychotic patients, and three (21%) of 14 definitely psychotic patients were classified as responders. The Mann-Whitney U test demonstrated a significant effect of psychotic status on response ($U=199.5$, $N=52$, $p<0.004$). A logit model (10) was fitted to the proportion of responders and nonresponders for the three levels of psychosis. Specifically, we hypothesized that psychosis predicted response such that the definitely psychotic group would be associated with nonresponse, the nonpsychotic group with response, and the probably psychotic group intermediate between the two. The traditional test of independence between these two variables (response and psychosis) was rejected ($\chi^2=8.9$, df=2, $p<0.01$). Additionally, the linear trend was highly significant (maximum likelihood estimate divided by the standard error= 2.77, $p<0.006$), thus supporting our linear hypothesis. Neither mean±SD baseline MAO activity (expressed as nanomoles of tyramine metabolized per milligram of platelet protein per hair) (definitely psychotic= 32.6±14.7, probably psychotic=35.4±11.3, and nonpsychotic=28.4±12.7) nor mean±SD percent change differed significantly among the three groups; most patients achieved 80% inhibition of platelet MAO activity by week 4 of treatment (definitely psychotic = 83.9%±16.4%, probably psychotic=76.0%±37.5%, nonpsychotic=84.6%±12.5%).

Next, we explored whether certain moderator variables correlated with psychosis, thereby explaining its effect on response. Specifically, since it has been suggested that poor response rate in psychotically depressed patients taking tricyclic antidepressants is a function of severity of illness (12), we examined the relationship of several indicators of severity to response rate. First, we used a series of chi-square tests and found no significant relationship between response and the various RDC subtypes (endogenous: $\chi^2=1.26$, df=1, $p<0.26$; recurrent: $\chi^2=0.00$, df=1, $p<0.97$; and incapacitating: $\chi^2=0.19$, df=1, $p<0.19$); sex ($\chi^2=0.00$, df=1, $p<1.0$); and initial dose ($\chi^2=0.01$, df=1, $p<0.93$). Second, to see if the relationship of psychotic status to response was also independent of these variables, we investigated this relationship only in patients classified according to the various RDC subtypes, sex, and initial dose and, as expected, found that the significance of the relationship between psychosis and response was slightly less than for the entire sample: endogenous ($U=127.5$, $N=39$, $p<0.06$), nonendogenous ($U=9.0$, $N=13$, $p<0.03$); recurrent ($U=78.5$, $N=30$, $p<0.07$), nonrecurrent ($U=25.5$, $N=22$, $p<0.01$); incapacitating ($U=82.0$, $N=36$, $p<0.007$), nonincapacitating (too few cases); male ($U=17.5$, $N=19$, $p<0.009$), female ($U=95.5$, $N=33$, $p<0.09$); 15 mg b.i.d. ($U=108.5$, $N=36$, $p<0.05$), 30 mg b.i.d. ($U=10.5$, $N=16$, $p<0.02$). In all subgroups, there was either a significant difference or a trend ($p<0.10$, two-tailed) indicating a poorer response to phenelzine in the psychotic group.

Finally, to examine the relationship between psychosis and response, adjusting for the effects of the moderator variables (RDC subtypes, overall severity, baseline Hamilton depression scale score, sex, and age), we used a multiple variable probit analysis (11), in which the outcome measure was response (dichotomously coded as responder or nonresponder) and the independent or predictor variables were the moderator variables. In each case, two predictor variables were included in the model, the first being one of the moderator variables and the second always being psychosis. In this way, we could examine the unique contribution of psychosis after removing the effect of each individual moderator variable. In all cases, the effect of psychosis on response remained significant (endogenicity: $\chi^2=7.47$, df=1, $p<0.006$; recurrence: $\chi^2=11.11$, df=1, $p<0.0009$; incapacitation: $\chi^2=7.07$, df=1, $p<0.007$; overall severity rating: $\chi^2=6.26$, df=1, $p<0.01$; baseline Hamilton scale score: $\chi^2=3.98$, df=1, $p<0.05$; sex: $\chi^2=6.38$, df=1, $p<0.01$; age: $\chi^2=4.03$, df=1, $p<0.05$). The p values of psychosis predicting response vary slightly because of the differing effects of each moderator variable. Given the large number of moderator variables and the limited sample size, we felt it inappropriate to use a single model that would include all the moderator variables simultaneously.

DISCUSSION

Our nonpsychotically depressed patients had a significantly better response rate to phenelzine than our psychotic patients, and the response rate of the probably psychotic patients fell between the rates of the other two groups. In a previous study (6) we performed a meta-analysis on more than 1,000 depressed patients treated with tricyclic antidepressants and found response rates of 67% in the nonpsychotic group and 35% in the psychotic group, a finding that closely parallels the differential response rate to phenelzine of our current group of 52 depressed patients. Recently, Spiker et al. (13) monitored plasma levels of amitriptyline and nortriptyline in 28 delusional depressed patients and found that those patients with combined levels above 250 ng/ml had a significantly better response rate than those patients with levels below; however, the overall response rate of their delusional patients was still much lower than that of the nondelusional patients.

Our present data indicate that patients treated with adequate doses (as reflected by percent of MAO inhibition) of phenelzine have a differential response rate similar to that of patients treated with tricyclics. We are unaware of any studies that have addressed the relationship between psychosis and response to phenelzine or any other MAO inhibitor. There was no placebo control group in this study or in most of the studies with tricyclic antidepressants; although our 16-day washout period to some degree allowed spontaneous improvement to occur, it did not fully control for this variable. Therefore, prospective, placebo-controlled studies will be needed to separate out two mechanisms: the difference in placebo improvement rates and the difference in specific drug improvement rates of psychotic and nonpsychotic patients. At the present time, our data suggest that treatment of psychotically depressed patients with a tricyclic antidepressant or with phenelzine alone will not suffice for the majority of this group and will probably require combined treatment with an antipsychotic drug or the use of ECT.

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Seasonal Affective Disorder in the Southern Hemisphere

Philip Boyce, M.B.B.S., F.R.A.N.Z.C.P., and Gordon Parker, M.D., Ph.D., F.R.A.N.Z.C.P.

To determine whether seasonal affective disorder exists in the southern hemisphere and whether there is any seasonal specificity in phenomenology, the authors compared 23 subjects who reported a winter/autumn affective disorder, consistent with earlier definitions of the syndrome, with 22 subjects who reported a spring/summer affective disorder. The subjects with winter/autumn onset were characterized by increased appetite, carbohydrate craving, and increased sleep; those with spring/summer onset reported decreased sleep and decreased appetite. Hypotheses concerning the etiology of seasonal affective disorder are discussed.

(Am J Psychiatry 1988; 145:96–99)

A relationship between seasons and depression has been proposed since the time of Hippocrates and Aretaeus (1). Over the past 15 years numerous studies (extensively reviewed elsewhere [2, 3]) have assessed seasonal variations in both depression and a consequence of depression, suicide. These studies have, in essence, found a greater chance of endogenous depression occurring in the spring and a lesser chance of it in the autumn.

A clinical observation that ran counter to the previous research—that some patients have a regularly occurring winter depression—led Rosenthal et al. (4), at the National Institute of Mental Health (NIMH), to examine whether a winter depressive syndrome existed. They recruited subjects through a newspaper article that described their preliminary observations. Their inclusion criteria specified subjects who had had a regular mood change in the winter, in at least 2 consecutive years, and whose depression remitted the following spring or summer. They identified a group of 29 subjects (mean±SD age=36.5±11.2 years), the majority (86%) of whom were women, who had a syndrome that the researchers subsequently termed "seasonal affective disorder." Rosenthal et al. (4) proposed the following operational criteria for the disorder: 1) a history of major affective disorder according to Research Diagnostic Criteria, 2) development of such depressive episodes in the autumn or winter and remission by the following spring or summer in at least 2 consecutive years, and 3) the absence of any other psychiatric disorder. Characteristic symptoms were increased appetite and weight gain, carbohydrate craving, decreased physical activity, and work and interpersonal difficulties, along with a depressed, anxious, and irritable mood.

Wirz-Justice et al. (5) screened subjects recruited through a magazine article in order to confirm the syndrome in Switzerland. They collected data on 22 subjects who met the diagnostic criteria specified by Rosenthal et al. (4). Demographically, the Swiss subjects were similar to the American subjects in terms of age (41.7 versus 36.5 years) and percent of women (73% versus 86%), and, like the American subjects (4), those in the Swiss group responded favorably to phototherapy.

We sought to determine whether such a syndrome exists in the southern hemisphere. If so, support would be given to the hypothesis that the syndrome is a consequence of the shorter photoperiod in winter and not due to other geophysical factors (such as the cold temperatures that were part of the environment of the previous studies) or even to social calendar factors associated with the northern hemisphere winter, such as Christmas. We also sought to determine whether such a syndrome was unique to winter or whether such a symptom pattern was a function of a seasonal depression per se, an issue not considered previously, since the subjects of the earlier studies were recruited on the basis of having a winter depression.

METHOD

Subjects were recruited through a popular women's magazine that carried an article describing several effects of weather on health, including the capacity of changing seasons (unspecified) to affect mood states. Readers were invited to participate in a research project if they had regular seasonal mood changes; again, symptom patterns were not specified. A questionnaire, based on the unpublished seasonal screening questionnaire developed by the NIMH researchers, was sent to all respondents.

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TABLE 1. Symptoms of Seasonal Affective Disorder in Two Studies

	Present Study					NIMH Study (4) (winter/autumn onset) (N=29)	
	Winter/Autumn Onset (N=23)		Spring/Summer Onset (N=22)				
Variable	N	%	N	%	χ^{2a}	N	%
Women	20	87.0	19	86.3		25	86
Men	3	13.0	3	13.6		4	14
Affect							
Sadness	18	78.3	15	68.2	2.06	29	100
Irritability	19	82.6	17	77.3	0.23	26	90
Anxiety	19	82.6	20	90.9	1.00	21	72
Worse in morning	8	34.8	10	45.5	2.53	—	—
Activity							
Decreased	20	87.0	19	86.3	2.04	29	100
Increased	2	8.7	2	9.1			
Appetite							
Increased	11	47.8	6	27.3	3.39	19	66
Decreased	8	34.8	12	54.5		8	28
Carbohydrate craving	18	78.3	14	63.6	2.81	23	79
Weight							
Weight increase	11	47.8	7	31.9	2.50	22	76
Weight decrease	7	30.5	10	45.5		5	17
Sleep							
Poor sleep quality	16	69.6	18	81.8	4.68	26	90
Sleep more	9	39.1	2	9.1	6.48	28	97
Sleep less	10	43.5	16	72.7			
Earlier bedtime	15	65.2	10	45.5	1.91	23	79
Early morning awakening	11	47.8	16	72.7	3.16		
Late morning awakening	11	47.8	5	22.7		22	76
Other							
Previous psychiatric treatment	19	82.6	19	86.3	1.45	20	69
Difficulties at menses	16	69.6	14	63.6	2.31	26	91
Work difficulties	22	95.7	22	100	0.97	28	97
Interpersonal difficulties	22	95.7	22	100	0.97	29	100
Decreased libido	15	65.2	12	54.5	3.31	20	69

[a] The groups did not differ significantly on any variable.

Following demographic inquiries, respondents were asked to describe their seasonal symptoms in narrative form. In addition, specific symptoms of any seasonal depression (or low energy state) were sought, including changes in activity level, appetite, weight, sleep pattern, and mood, as well as any diurnal mood variation or deterioration of interpersonal relations. Carbohydrate craving during the depressive state was specifically examined. We also sought details on any past history of migraine, light sensitivity, drug or alcohol difficulties, psychiatric treatment, and medication.

RESULTS

The questionnaire was sent to 323 individuals, 138 of whom returned it fully completed for subsequent analysis. The mean±SD age of the sample was 41.8±14.4 years. Eleven (8%) were men and 127 (92%) were women. The majority of respondents (73%, N=101) came from Victoria and New South Wales, the most populous states in Australia. Eighty subjects reported depressive symptoms associated with a particular season; the remainder (N=58) reported no seasonal symptoms. Of the group with seasonal symptoms, only eight (10%) were men. Twenty-eight subjects (35%) had depressive symptoms in the winter, 28 (35%) in the summer, 16 (20%) in the spring, and only eight (10%) in the autumn.

Subjects were considered further only if they had had three or more mood change episodes in the same season over the past 5 years. After imposing these criteria, we were left with 23 subjects with onset of symptoms in winter or autumn (mean age=39.5± 13.4 years) and 22 subjects whose symptoms emerged in spring or summer (mean age=44.4±13.4 years). We so divided our subjects because seasonal affective disorder has previously been defined as having its onset in autumn or winter, which implies that the seasonal affective disorder symptom complex is confined to those seasons. We compared our two groups to determine whether symptoms were "season specific." If the symptom pattern was season specific, we anticipated differences in the symptom pattern between groups. On the other hand, if the symptoms were more a function of seasonality alone, then there should be no differences between the groups.

The subjects with winter/autumn seasonal affective disorder had a symptom pattern similar to that found in previous studies of seasonal affective disorder (table 1). They reported irritability, anxiety, and sadness; like the subjects in the American study of seasonal affective disorder (4), they also reported decreased activity, increased appetite, carbohydrate craving, earlier bedtime and later awakening, work and interpersonal difficulties, and decreased libido.

We compared our groups with winter/autumn and spring/summer onset by using the chi-square test. While the frequencies of symptoms did show some differences, the differences were not significant. There was a trend for those with winter/autumn onset to sleep more, go to bed earlier and wake later, have an increase in appetite and crave carbohydrates. By contrast, the group with spring/summer onset slept less, woke earlier, and had a decrease in appetite and weight, and their mood was worse in the morning.

DISCUSSION

We report a study of southern hemisphere subjects who suffer from a seasonal disorder that has its onset in winter/autumn and remits in spring/summer. Our sample contained a preponderance of women, hardly surprising since the subjects had been recruited through a women's magazine. The symptom pattern and demographic characteristics (sex ratio and mean age) of our sample are remarkably similar to those reported in previous northern hemisphere studies of seasonal affective disorder. We also identified a group of subjects who reported a seasonal disorder with an onset in spring/summer and remission in autumn/winter, as described by Wehr et al. (6). These subjects had a slightly different symptom pattern. Until our findings are replicated, it remains unclear whether such a pattern reflects another seasonal syndrome or a seasonal effect on depressive symptoms.

We attempted to determine whether key symptoms are a function of seasonality alone (annual periodicity), or are related to winter itself, by examining differences between the two seasonally separate groups. While there was a trend for the groups to differ on several symptoms, such differences were not significant, perhaps a consequence of the small sample size leading to a type II error. Our findings are therefore equivocal in that the symptom patterns of our two groups were neither sufficiently similar nor dissimilar to tell us whether they were due to a specific season.

If the symptom complex of seasonal affective disorder is unique to winter/autumn, then it is pertinent to consider possible environmental factors that may contribute to its onset, especially when studies have been conducted in countries with distinctly different winter climates. In Australia, the winter is milder than in countries represented in previous reports. For instance, Rosenthal et al. (4) reported a mean midwinter temperature of less than 30°F in Rockville, Md., while in Australia, the temperature rarely falls to the freezing point. This would suggest that temperature is not a climatic variable contributing to the onset of the disorder. More relevant is the similarity in the mean day length (sunrise to sunset) in midwinter between Australia (i.e., June) and Rockville, Md. Because the majority of the subjects with winter/autumn onset (73%) came from the adjoining states of New South Wales and Victoria, the mean midwinter photoperiod of Sydney (590 minutes) is likely to be representative of most of our subjects. The mean midwinter photoperiod in Rockville, Md., the key center in the American study (4), is approximately 560 minutes. Since Australia is closer to the equator than Rockville, Md., the amplitude of the photoperiod is lower, with the maximum day length in Sydney being 866 minutes, compared to approximately 900 minutes in Rockville. The similarity in the midwinter photoperiod between Sydney and Rockville, along with the differences in temperatures, offers some support for the hypothesis that the photoperiod is an important environmental variable associated with seasonal affective disorder.

That day length may be a critical variable in the onset of seasonal affective disorder is supported by the fact that bright artificial light in the evening or morning has an ameliorating effect on patients with the disorder (4, 5, 7–10). Additional support comes from an open study (11) in which nine subjects with seasonal affective disorder and eight subjects with nonseasonal depression were treated with phototherapy. Phototherapy was only effective in reducing depressive symptoms in the group with seasonal affective disorder and had no effect on the subjects with nonseasonal depression; this finding suggests the specificity of light in seasonal affective disorder.

If it is conceded that seasonal affective disorder is related to the short photoperiod of winter and that the disorder responds uniquely to phototherapy, a disturbance in melatonin secretion from the pineal gland is suggested, since melatonin secretion is under photoperiodic control and light suppresses its secretion (12). While the melatonin hypothesis is appealing, there is little confirmatory evidence. Initially, phototherapy was considered to have its effect by simulating the photoperiod of summertime, but this has not been substantiated. A study comparing two bright-light conditions (13), one from 7:30 a.m. to 10:30 a.m. and 8:00 p.m. to 11:00 p.m. (increasing the photoperiod) and the other from 9:00 a.m. to noon and 2:00 p.m. to 5:00 p.m. (providing no increase in photoperiod), found that both lighting schedules were equally effective in treating seasonal affective disorder. The authors of that study concluded that "the results do not appear to support the hypothesis that phototherapy acts via a photoperiodic mechanism in which the timing of light relative to a putative nocturnal photosensitive interval is critical" (p. 873). Further, they considered that suppression of melatonin secretion was unlikely to mediate the antidepressant effect of light. More recently, Lewy et al. (14) have proposed that circadian rhythms in seasonal affective disorder are abnormally phase-delayed and were able to demonstrate such a phase-delay in eight patients with winter depression. They found that phototherapy in the morning, which would have an effect in advancing the melatonin circadian rhythm, was more effective in reducing depression than evening phototherapy. They also found that the morning phototherapy corrected the phase-delay of melatonin found in the patients with winter depression. These findings provide support for a phase-delay hypothesis for seasonal affective disorder.

In conclusion, our study suggests that seasonal affective disorder associated with autumn/winter exists in the southern hemisphere and has a symptom pattern similar to that found in the northern hemisphere. While the exact mechanism for this disorder remains unclear, adaptation to the short photoperiod of winter is likely to be of importance in the genesis of the disorder. We have also identified a group of subjects with a seasonal disorder associated with spring/summer, a finding that requires replication before any possible mechanisms for such a disorder can be proposed.

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Comparison of Seasonal and Nonseasonal Affective Disorders

Michael J. Garvey, M.D., Robert Wesner, M.D., and Michael Godes, R.N.

Eighteen patients with seasonal affective disorder were compared to 13 patients with recurrent nonseasonal depressions. Seasonal depressions were associated with hypersomnia and carbohydrate craving, and there was a trend for a younger age at onset of seasonal affective disorder.

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Some patients with recurrent depressions have a regular seasonal onset to their depressions. Such individuals are described as having seasonal affective disorder. Their depressive episodes usually begin in the fall or winter and remit in the spring or summer (1). The prevalence of seasonal affective disorder is unknown (2).

Patients with seasonal affective disorder have been characterized as having atypical depressive symptoms, such as hypersomnia, increased appetite, and carbohydrate craving (2, 3). A high percentage of such patients have also been reported to have irritability, anxiety, fatigue, decreased libido, difficulty concentrating, and premenstrual dysphoria (2, 3). We hypothesized that these symptoms would be more common in patients with seasonal affective disorder than in patients with recurrent nonseasonal depressions.

On the basis of preliminary information gathered from patients with seasonal affective disorder, we also hypothesized that during remission of the affective disorder, such patients would be more likely to have seasonal changes in their sleep, seasonal changes in their craving of carbohydrates, and dysphoria during the winter or during cloudy days than would patients with recurrent nonseasonal depressions or non-ill control subjects. We tested these hypotheses by comparing patients with seasonal affective disorder to patients with recurrent nonseasonal affective disorder and to non-ill control subjects.

METHOD

Consecutive patients were selected from a private practice outpatient clinic. All patients were given a semistructured diagnostic interview by one of us (M.J.G.). Patients who were diagnosed as having major depression (*DSM-III*) and consented to participate in the study were given a structured interview that elicited information about depressive symptoms, such as insomnia, hypersomnia, appetite change, carbohydrate craving, fatigue, irritability, anxiety, dysphoria, difficulty concentrating, and decreased libido. Patients were also asked whether they experienced seasonal changes in their sleep, seasonal carbohydrate craving, wintertime dysphoria, or dysphoria on cloudy days when their affective disorder was in remission. Female patients were asked whether they had regular premenstrual dysphoria during remissions.

Longitudinal psychiatric histories were obtained from all depressed patients. Patients were considered to have a seasonal affective disorder if they had two or more major depressive episodes starting during the same season of the year and no major depressions starting at other times of the year. Nonseasonal affective disorder was defined as recurrent major depressions starting at different seasons of the year. Patients who had 10 or more lifetime depressive episodes were considered to have had a seasonal affective disorder if at least 90% of their depressions started during the same season.

Patients with a single episode of major depression were not included in the data analysis. There was no way to tell if such patients would go on to have recurring depression and whether such recurrences would be of a seasonal or nonseasonal character.

Control subjects were selected from a psychiatry department support staff. After an explanation of the project, subjects were asked to anonymously fill out a questionnaire that included the Beck Depression Inventory (21 depression items) and questions relating to seasonal sleep changes, seasonal carbohydrate craving, wintertime dysphoria, cloudy day dysphoria, and premenstrual dysphoria. Control subjects who felt they might be currently depressed were asked to decline participation in the study by simply not returning the questionnaire. Control subjects were also asked whether they had ever experienced a major depression

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in the past. Only those subjects who denied both past and current depressions and who had a Beck Depression Inventory score of less than 10 were used as non-ill control subjects for comparison purposes.

Chi-square analyses were used for comparisons of categorical variables. The Fisher exact test was used if the expected frequency for 25% of the chi-square cells was less than five. Continuous variables were compared by the Student t test if the sample was normally distributed and by the Wilcoxon rank sum test for samples not normally distributed. Comparisons of continuous variables involving more than two groups were analyzed by an analysis of variance, followed by individual Student t tests when appropriate. Multiple comparisons of continuous variables with unequal numbers of subjects were analyzed with the least square means procedure of the Statistical Analysis System program. To protect against a type I error, the Bonferroni correction was employed when multiple comparisons were made.

RESULTS

Forty-seven patients met the study criteria, and all agreed to participate. Eighteen patients (38%) had recurrent depressions with distinct, consistent seasonal onsets. The season of depression onset for these 18 patients was most often fall or winter (72%, N=13). Thirteen of the 47 patients (28%) had recurrent depressions but with no regular seasonal onset pattern. Questionnaires were given to 96 control subjects. Ninety-one percent (N=87) responded. Sixty-one subjects gave no evidence of past or current depressions. Table 1 illustrates comparisons between the control subjects, patients with seasonal affective disorder, and patients with recurrent, nonseasonal depressions. The mean±SD ages of the three groups at interview were 37±9, 37±12, and 45±10 years, respectively. There was a significant difference in age between patients with nonseasonal depression and patients with seasonal depression (t=2.25, df=89, p<0.027) and control subjects (t=2.73, df=89, p<0.008).

Hypersomnia and carbohydrate craving were more common in patients with seasonal depression than in those with nonseasonal depression. Reduced libido, irritability, and increased appetite were somewhat more common in patients with seasonal depression but not significantly so. Depressive symptoms such as insomnia, appetite loss, fatigue, anxiety, difficulty concentrating, and dysphoria were present in a high percentage of patients with seasonal depression but were equally common in patients with nonseasonal depression. During times when a major depression was in remission, there was no significant difference between patients with seasonal or nonseasonal affective disorder in premenstrual dysphoria, cloudy day dysphoria, wintertime dysphoria, seasonal sleep changes, and seasonal carbohydrate craving. However, all of these items were slightly more common in patients with seasonal affective disorder. During remissions from major depression, the latter patients were more likely to experience seasonal sleep changes than were the control subjects (p<0.02, table 1); the difference was not statistically significant after the Bonferroni correction for multiple comparisons was applied. Patients with seasonal or nonseasonal affective disorder were also much more likely to experience cloudy day dysphoria than were the control subjects (table 1).

There was a trend for patients with seasonal depression to have an earlier illness onset (mean±SD age=22±11 years versus 29±11 years; p<0.14). The patients with seasonal or nonseasonal depression did not differ significantly in the number with a past history of either mania or hypomania.

TABLE 1. Characteristics of Patients With Seasonal Affective Disorder or Recurrent Nonseasonal Depression and of Normal Control Subjects

	Patients With Seasonal Depression (N=18)		Patients With Nonseasonal Depression (N=13)		Control Subjects (N=61)	
Characteristic	N	%	N	%	N	%
Women	11	61	8	62	38	62
Men	7	39	5	38	23	38
Past history of mania	4	22	2	15		
Past history of hypomania	6	33	3	23		
Family history of alcoholism	6	33	4	31	—	—
Family history of affective disorder	10	55	6	46	—	—
During depression						
Hypersomnia[a]	13	72	2	15		
Carbohydrate craving[b]	12	67	3	23		
Reduced libido	12	67	5	38		
Increased appetite	9	50	4	31		
Irritability	14	78	7	54		
Fatigue	17	94	11	84		
Anxiety	16	89	10	77		
Reduced concentration	15	83	12	92		
During remission						
Seasonal sleep changes[c]	8	44	3	23	9	15
Seasonal carbohydrate craving	5	28	2	15	13	21
Premensrual dysphoria	6	55	3	38	24	39
Wintertime dysphoria	4	22	2	15	19	31
Cloudy day dysphoria[d]	8	44	4	31	2	3

[a] Significant difference between patients with seasonal and nonseasonal depression ($\chi^2=9.76$, df=1, p<0.002).

[b] Significant difference between patients with seasonal and nonseasonal depression ($\chi^2=5.78$, df=1, p<0.02).

[c] Significant difference between patients with seasonal depression and control subjects (p<0.02, Fisher's exact test).

[d] Significant difference between control subjects and patients with seasonal (p<0.001, Fisher's exact test) and nonseasonal (p<0.008, Fisher's exact test) depression.

DISCUSSION

Some parts of the study hypotheses were confirmed, whereas other parts were not. Patients with regular seasonal onset of depression were more likely to have had hypersomnia and carbohydrate craving with major depressive episodes than were patients with recurrent nonseasonal affective disorder. We were unable to demonstrate that the symptoms of irritability, anxiety, fatigue, increased appetite, difficulty concentrating, or decreased libido were more common in patients with seasonal depression than in those with recurrent nonseasonal depression. While a majority of our patients with seasonal affective disorder had these symptoms, they occurred with nearly equal frequency in the patients with nonseasonal affective disorder. Possibly both groups of patients could have differences in the quality or severity of these various depressive symptoms. In addition, larger sample sizes may demonstrate that certain clinical features such as decreased libido are, in fact, significantly different in populations with seasonal or nonseasonal depression.

We were unable to demonstrate that during remission of affective disorder, patients with seasonal depression were significantly more likely than patients with nonseasonal depression to show seasonal changes in sleep or carbohydrate craving or in dysphoria associated with cloudy days, wintertime, or the premenstruum. However, all of these symptoms tended to be slightly more prevalent in patients with seasonal affective disorder. Compared to non-ill control subjects, patients with seasonal depression were more likely during remission to show seasonal sleep changes and cloudy day dysphoria.

The majority of the patients with seasonal affective disorder were bipolar; however, the proportion was not significantly greater than that in the patients with nonseasonal affective disorder (55% versus 38%). Mania and hypomania were diagnosed by history. Mania is likely to be underrepresented with such a retrospective diagnosis (4), and the same may be true for hypomania. However, this diagnostic underrepresentation should have been true for both patient groups.

Sharper distinctions between the two patient groups may at times be confounded by the contamination of the nonseasonally depressed group with "true" seasonally depressed patients. There are two case reports in the literature which indicate that a patient with a strong seasonal tendency for onset of depression over many years may occasionally shift to a different season (5, 6). Patients who shift seasons would be counted as having nonseasonal affective disorder in a study such as ours but yet would have "true" seasonal affective disorder.

We made multiple comparisons between study groups. It could be argued that positive findings with low levels of significance were merely chance findings. For several of our positive findings (table 1), this argument is not valid because we specifically tested for such items as hypersomnia, carbohydrate craving, and cloudy day dysphoria on the basis of previous positive findings by other investigators (2, 3).

The prevalence of seasonal depression in our study patients (38%) is higher than that previously reported (2, 7). If only patients with fall/winter depressions (28%) are counted, the prevalence is close to the 23% reported by Rosenthal et al. (2). These figures do suggest that seasonal affective disorder is not uncommon.

At present it is not clear if seasonal affective disorder represents a distinct depression subtype. Data from this study and others suggest that patients with the disorder do experience certain phenomena not usually found in other depressions. In addition to the presentation of a seasonal depression pattern, these patients also have a relatively high frequency of hypersomnia and increased appetite. These symptoms are not found in most depressions (8). Patients with seasonal affective disorder appear to be quite sensitive to phototherapy (2, 3, 9). Preliminary evidence of the effectiveness of phototherapy for unselected cases of depression may be less impressive (10). Patients with seasonal affective disorder may also have a younger age at illness onset (2, 3). These various findings are consistent with the hypothesis that such patients do represent a distinct subtype of depression.

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Psychiatrist-Executive Management Styles: Nature or Nurture?

Luis R. Marcos, M.D., and Michael A. Silver, M.D.

The authors studied the management styles of the 11 directors of psychiatry in municipal general hospitals in New York City. The Lead-Self Scale and the Lead-Other Scale were used. The directors' Lead-Self Scale scores were compared with those of 11 psychiatric residents. Results show that the directors had a high task/high relationship primary style and a high relationship/low task secondary style. Psychiatric residents revealed a less differentiated pattern of self-perceived management style. The authors speculate about the effects of experience, training, role models, and personality traits on management styles and suggest areas for further research.

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Administration, according to Milton Greenblatt (1), is "a vital component of the practice of psychiatry." Whether they are chiefs of departments or heads of interdisciplinary clinical teams, psychiatrists in executive positions need the cooperation of other clinicians, administrators, and support staff to effectively provide, among many services, discharge planning, clinical documentation, or the evaluation and treatment of patients in a timely and cost-effective fashion. Recent developments in prospective payment systems that emphasize clinical diagnosis and length of hospital stay as the major determining variables for reimbursement have highlighted the role of the psychiatrist-executive not only in the management of patients but also in maintaining the financial solvency of the institution (2).

The purpose of this study was to ascertain the management styles of a group of directors of departments of psychiatry in large general hospitals in New York City and compare their self-perceived management styles with the self-perceived management styles of psychiatric residents who had no formal managerial experience. Although professional and personality aspects of the psychiatrist-executive have been described in the literature (1, 3–7), the study of psychiatrists' management styles has been limited (1, 8).

As part of their managerial role, directors of psychiatry are required to participate in decision-making processes concerning the planning and monitoring of their services as well as to recruit capable staff. Psychiatrists in executive positions are expected to be innovative and implement new psychiatric knowledge and techniques. They operate in a system that, apart from the human element, is composed of many interrelated subsystems, including the academic, clinical, and administrative components of the hospital. Most importantly, psychiatrist-executives are to provide leadership and integrate the different subsystems and components of the department.

Management, as described in 1911 by Frederick W. Taylor in his scientific management model (9), was to be divorced from human relations and emotions to enhance efficiency and increase production. This model emphasized task-oriented behavior by managers. In the 1930s, a different trend was started by Elton Mayo (10). His theory argued that in addition to the need for technological factors to improve output, it was important for managers to be concerned with human affairs. This human relations model focused on people—their feelings and attitudes. In essence, this movement stressed relationship-oriented behavior by managers.

In 1960, McGregor's theory X and theory Y (11) defined the worker as either disliking work and requiring coercion to produce or enjoying work and requiring a nurturing atmosphere. A shift from these values started sometime in the 1970s with the beginning of the economic recession. Proponents of management theories began to reevaluate the humanistic model (12). As the Western business world became acquainted with Japanese theories of management, which emphasize work culture and group focus (13), a further decline of the hierarchical structure came to the forefront.

The more recent situational model of management is the result of the development and interrelation of the "scientific" and "human relations" models of management (14). This approach is distinctive because it does not depict a single ideal management style as being appropriate in all situations. Rather, it allows effective

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TABLE 1. Management Style Scores of 11 Direc[illegible] Hospital Psychiatry Departments and 11 Psychiatry Residents

	Score of Directors of Psychiatry				Score of Residents for Self-Perception	
	Self-Perception		Others' Perception			
Management Style[a]	Mean	SD	Mean	SD	Mean	SD
High task/low relationship	1.27	0.61	1.82	0.39	2.00	0.60
High task/high relationship	7.09	0.79	7.00	1.04	4.36	0.64
High relationship/low task	2.73	0.75	2.45	0.78	3.82	0.93
Low relationship/low task	0.91	0.67	0.73	0.45	1.82	0.71

[a] See text for definitions.

managers to adjust their managerial styles in relation to the degree of maturity of subordinates and the nature of the working environment. This model is particularly useful for the study of more heterogeneous and complex organizations such as hospitals. For the purpose of this study, management is defined according to the situational model as working with and through people to accomplish the institution's goals.

METHOD

The 11 directors of psychiatry in New York City's municipal general hospitals participated in the study. These hospitals' psychiatric services include acute-care inpatient psychiatry as well as alcohol and substance abuse services. The hospitals also provide comprehensive outpatient services including psychiatric clinics, emergency rooms, and day hospitals. The size of the hospitals and the scope of their services vary. Most have an academic component, including residency training programs and research, which also lies within the administrative responsibilities of the director of psychiatry.

The participating directors were psychiatrists with many years of experience in hospital psychiatry leadership positions. They were all men, and their mean age was 53 years, ranging from 44 to 66 years. All were Board certified in psychiatry, and two also held certificates in psychiatric administration. Six were Fellows of the American Psychiatric Association. Their academic rank ranged from associate to full professor (four associate professors and seven professors).

To ascertain their management styles, we used the Lead-Self Scale and the Lead-Other Scale developed by Hersey and Blanchard (14). These instruments measure the manager's style and are based on the model of situational leadership. The Lead-Self Scale defines the manager's self-perception of his or her management style and behavior. The Lead-Other Scale reflects the perception of the manager by others familiar with him or her and the organization's working environment.

Styles are determined by four "ipsative" scores; that is, each style is not scored independently. The highest possible rating for each style is 12 points, and high scores in one style result in lower scores in the others. The instruments have been standardized according to the responses of many managers. Validity studies (14–16) have shown that these scales are empirically sound instruments.

The instruments measure four basic styles: 1) high task/low relationship (the manager defines roles and tells subordinates what, how, when, and where to do the various tasks and closely monitors their performance), 2) high task/high relationship (the manager provides direction and explains decisions but also "sells" the ideas and provides opportunity for clarification and psychological support), 3) high relationship/low task (both the leader and the follower participate and share in decision making), and 4) low relationship/low task (the manager delegates, turns over the responsibility for decisions and implementation, and provides little direction or support). Twelve situations are presented, and the respondent is asked which of these four styles would characterize his or her management style in each situation.

The 11 directors of psychiatry participating in this project completed a Lead-Self Scale. They were not familiar with this instrument nor with the purpose of the study. Concomitantly, health care program analysts familiar with the daily functioning of the service and the style of each director completed a Lead-Other Scale. This was done to ascertain whether there was a discrepancy between the directors' self-perception of their management styles and the perception of others.

To contrast the directors' management styles with those of nonexperienced psychiatrists, a randomly selected group of 11 psychiatric residents (in their second postgraduate year) also completed the Lead-Self Scale.

RESULTS

The mean ± SD scores for each style are presented in table 1. The scores of the directors of psychiatry on the Lead-Self Scale revealed that, both individually and as a group, they perceived their primary management style to be high task/high relationship. Their mean score for this style accounted for 59.1% of their overall score. This style was followed by a high relationship/low task style (22.8%), high task/low relationship (10.6%), and low relationship/low task (7.6%).

To ascertain whether the directors' self-perceived style was consistent with the perception of health care program analysts familiar with the daily functioning of the service and the style of each director, the Lead-Other Scale ratings for each director were analyzed. The results show that others perceived the same primary management style in each director: high task/high relationship. The mean score for this management style for all directors constituted 58.3% of their total score. Also, as with the Lead-Self results, it was followed by high relationship/low task (20.4%), high task/low relationship (15.2%), and low relationship/low task (6.1%). These ratings showed that there was overall agreement between the directors' self-perceived management styles and their styles as perceived by others.

The analysis of the Lead-Self Scales completed by the residents showed that although their ratings of their general pattern of management style were similar to the directors' self-ratings, the residents did not have as distinct and differentiated management styles. Specifically, residents perceived their primary management style to be high task/high relationship, but their mean score for this style accounted for 36.3% of their overall management style. High relationship/low task contributed 31.8%, high task/low relationship contributed 16.7%, and low relationship/low task contributed 15.2%.

DISCUSSION

Before elaborating on the results, we should note that this study has important limitations. These include a small sample, the fact that the participants were drawn from a single geographic area and a single type of work setting, the use of a single rating scale, and the lack of any direct correlation between the management styles and any objective criteria of success.

Our directors of psychiatry emphasized a high task/high relationship management style as their primary style and a high relationship/low task as their secondary style. Together, these styles accounted for 82% of the directors' overall management behavior as perceived by themselves and 79% as perceived by others. Both styles have in common their high relationship component.

This finding is consistent with the attitudes of prospective psychiatrists. A review of the factors in medical students' choice of psychiatry as their professional specialty (17) showed that students planning a career in psychiatry are highly person oriented. Psychiatrist-administrators appear to maintain this attitude and are especially responsive to the humanistic value system. They tend to emphasize interpersonal approaches to management while disavowing the use of power-related behaviors (5, 18, 19). Some have suggested that this orientation may be related, at least in part, to their clinical training in psychiatry (1, 4–6, 18, 19).

Generally, the literature shows that managers who use predominantly the high task/high relationship style and have a high relationship/low task secondary style may find it difficult to delegate to subordinates even if they are competent. They also tend to do well with subordinates of average levels of maturity (average knowledge and skills in performing the tasks and motivation and commitment to the task) but may find it difficult to handle discipline problems, immature work groups, or unstable organizations (14, 18). These situations may require a high task/low relationship style to make rapid decisions, enforce critical changes without delay, and minimize time-consuming reflections.

The high task/high relationship style is considered a "safe style" because even when inappropriately used, it has less chance to result in a crisis. This style is effective with people who are unable but willing to take responsibility and who are confident but lack certain skills at any given time. This style has been referred to in the situational model (14) as a "selling style." It emphasizes two-way communication while the manager tries to get the subordinates psychologically to "buy into" desired behaviors.

Although we are not aware of any study linking a particular management style with success in hospital psychiatry, there is some indirect evidence suggesting that high relationship management styles may be generally useful in psychiatric organizations, particularly in stable organizations that are not under substantial internal strife or pressure (18). As Greenblatt (1) pointed out, psychiatric services function more on the basis of [illegible] and mutual agreements and relationships [illegible] on the basis of pyramidal authority. Furthermore, psychiatrists often view administration as a social process and the organization primarily as an interaction of human beings more than one of technology or policy. On the other hand, the recent increasing financial pressure on hospital psychiatry and clinical decision making may make high relationship management styles less desirable.

We do not know the variables responsible for the directors' management style, nor can we account for the differences between their style and that of resident psychiatrists. However, we can reasonably speculate about the possible effects of several factors. One possibility is that the management styles of these directors of psychiatry were the result of learned managerial theory and knowledge through self-education and experience in both administration and clinical psychiatry (20, 21).

A second factor to be considered is the effect of role models or mentors on a developing administrator. Many psychiatrist-executives acknowledge the influence of teachers and mentors on their administrative development. Mentor relationships can impart expert knowledge, evaluate and reinforce appropriate management styles, and model effective and efficient leadership behavior (22, 23). In addition, there is evidence that formal training in management has a positive impact on the style and effectiveness of future psychiatric administrators (24, 25). And in more recent years, there has been an emphasis on the teaching of administration, management, and policy making to psychiatric residents (26–28).

Some educators still support the belief that psychiatrists learn their management skills by trial and error and that these skills cannot be taught. In fact, for many years, a common approach to the study of management assumed certain "nonteachable" personality traits, such as physical energy, determination, and intelligence, as being the essentials of effective management (4–7). Only individuals with these inherent personal qualities were considered potentially good managers.

Further research is needed to elucidate the question of what factors contribute to the development by psychiatrist-executives of distinct management styles. Specifically, there is a need to study the relationships among management style, personality traits, formal administrative training, managerial experience, clinical training and experience, and the influence of mentors or role models. Also, it is important to ascertain the effects of specific management styles on subordinates' morale and productivity, on the quality of patient care, and on the level of accomplishment of organizational goals.

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Clinical and Research Reports

Self-Care Capacity and Anticholinergic Drug Levels in Nursing Home Patients

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The serum anticholinergic levels of 22 demented nursing home patients were related to their cognition and capacity for self-care. The patients with high anticholinergic levels had greater impairment in self-care capacity than patients with low levels.

(Am J Psychiatry 1988; 145:107–109)

Elderly patients in nursing homes take more medications than elderly persons in the community, and these medications may be prescribed in potentially toxic doses (1, 2). Drugs frequently responsible for toxicity include anticholinergic medications, which block CNS cholinergic receptors (3). This can interfere with memory and cognition and may increase the disability of demented patients by worsening their already compromised cognitive functioning (4, 5). We measured serum anticholinergic drug levels in nursing home patients to determine if anticholinergic levels were related to cognition and capacity for self-care.

METHOD

The nursing home was a 181-bed proprietary intermediate-care facility in Baltimore. The demographic characteristics of its patients are comparable to those of other nursing home patients in Maryland (6). Letters explaining the study were sent to the families and physicians of all 181 residents. Inclusion of a patient in our study required the consent of the patient, a family member, and the physician; 22 patients met these criteria.

The demographic characteristics and diagnoses of the sample did not differ significantly from a random sample of other residents in the home (6). There were 17 women and five men, all were white, and the mean±SD age was 80.8±9.6 years. Eleven met the *DSM-III* criteria for primary degenerative dementia, nine had multi-infarct dementia, one had Korsakoff's syndrome, and one had a seizure disorder with cognitive impairment.

The patients took an average of 2.7 drugs per day, and their doses were within the usual clinical ranges. The medications reflected prescribing patterns in other nursing homes except that fewer medications were given than have been reported in other nursing homes (7). This was probably a result of the active pharmacy review service in this nursing home.

The patients' medication schedules and clinical histories were obtained by chart review. A research psychiatrist (B.W.R.) examined each patient to determine physical, neurological, and mental states and make *DSM-III* diagnoses. Limitation in mobility due to arthritis, stroke, or extrapyramidal symptoms was noted. The Mini-Mental State examination (8) was used to quantitate cognitive impairment. To determine the self-care capacity of each resident, the member of the nursing staff most familiar with the patient was interviewed and asked to rate the patient on the self-care subscale of the Psychogeriatric Dependency Rating Scales (9).

After the clinical examination, blood was drawn for determination of serum anticholinergic level by means

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TABLE 1. Clinical Features of Nursing Home Patients With Serum Anticholinergic Levels Below and Above the Median (0.83 pmol/ml)

	Patients' Anticholinergic Level				Significance		
	Below Median (N=11)		Median or Above (N=11)				
Feature	Mean	SD	Mean	SD	t	df (pooled variance)	p
Age (years)	80.2	8.4	81.5	11.0	−0.3	18.7	0.7
Mini-Mental State score	6.3	9.6	5.2	2.1	0.3	18.1	0.7
Self-care score[a]	13.2	8.3	20.1	1.5	−2.4	16.4	0.03
Total number of drugs	2.2	1.3	3.1	1.6	−1.5	19.0	0.2
Number of anticholinergic drugs	1.0	0.0	1.0	0.0	−2.4	16.4	0.03

[a] From the Psychogeriatric Dependency Rating Scales (9).

of a radioreceptor assay with known reliability and validity (5). The blood samples were obtained approximately 4 hours after medications were last given.

RESULTS

A wide range of anticholinergic levels was found (0.0–9.95 pmol/ml; median=0.83 pmol/ml). We compared the patients with anticholinergic levels above and below the median level. There was no significant difference between the two groups in prevalence or type of dementia, prevalence of arthritis, or sex. Table 1 presents other clinical features of the two groups. The patients with anticholinergic levels above the median had a significantly higher score on the self-care subscale of the Psychogeriatric Dependency Rating Scales. A higher score reflects greater disability in dressing, personal hygiene, mobility, toileting, and urinary continence. Anticholinergic level was significantly correlated with self-care score ($r=0.42$, $df=20$, $p<0.025$).

DISCUSSION

The study sample was small and depended on family members' responses to mailed consent forms explaining the study. The family members who consented to the study may have been concerned about the medications their relatives were receiving. However, the demographic characteristics, medications, and prevalence and type of dementia of the patients studied were similar to those of the other patients in the same nursing home. This suggests our sample is representative of other patients in this nursing home.

The radioreceptor assay measured the total serum anticholinergic activity of each patient's drug regimen. This analysis was desirable because many medications have anticholinergic activity. We believe that the levels measured represented steady-state measures because the medications had been given regularly during the preceding week and the blood samples were taken about 4 hours after the last medications were given.

Anticholinergic activity levels could not be predicted by the total number of drugs, the number of anticholinergic drugs, or drug doses. This is probably because many drugs have unrecognized anticholinergic activity and because individuals differ considerably in their absorption, metabolism, and excretion of drugs. In fact, anticholinergic levels may vary 10-fold among individuals taking identical doses of the same anticholinergic medication (5).

High anticholinergic levels were associated with greater impairment in self-care capacity. Impaired self-care may be due to dementia, paresis from stroke, limitation from arthritis, akinesia from neuroleptics, or some cumulative effect of multiple medications. However, the patients with high anticholinergic levels did not differ from those with low levels by type of dementia, limitation by stroke or arthritis, use of neuroleptics, age, or sex. The Mini-Mental State scores were uniformly low and did not differ between the two groups. Therefore, the severity of dementia cannot explain the observed difference in self-care capacity either. We do not believe the medical conditions of the patients with high levels required treatment with more anticholinergic drugs, because the medical conditions and number of anticholinergic medications were similar in the two groups.

Anticholinergic drugs are known to cause global disruptions in cognition (4, 5) and may be responsible for the greater impairment in self-care capacity in our patients with high anticholinergic levels. A prospective, controlled trial is needed to test this hypothesis. Such a study would measure self-care capacity before and after reduction of anticholinergic medications to determine if self-care improved when anticholinergic levels declined.

The major implication of this study is that anticholinergic medications may be associated with excess disability in nursing home patients. Nursing homes are health care systems in crisis: many patients have progressive disabilities, medical care is limited, and the cost of care is increasing. Therefore, it is imperative to find ways to reduce disability. The review of patients' medications may be an effective first step.

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The Role of External Heat Load in Triggering the Neuroleptic Malignant Syndrome

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During a heat wave three patients developed neuroleptic malignant syndrome. The role of heat load in triggering this syndrome and possible mechanisms behind such a role are discussed. Data concerning the season of occurrence of neuroleptic malignant syndrome are reported.

(Am J Psychiatry 1988; 145:110–111)

During a heat wave in the summer of 1985 three patients, representing 4% of all admissions to our hospital from June to September, developed neuroleptic malignant syndrome, and one of them died. The weather conditions were extreme: the temperature ranged from 30°C (86°F) at night to 36°C (97°F) during the day, and the humidity exceeded 70%. The climatic conditions in our region are usually more tempered; the mean temperature for August is 26°C to 28°C (79°F to 82°F), and for January it is 12°C to 14°C (54°F to 57°F). The past prevalence of neuroleptic malignant syndrome in our unit (based on a 14-year survey) is 0.4% (1). We were intrigued by this occurrence and looked for data that could substantiate a possible correlation between heat load and neuroleptic malignant syndrome.

Heat load is defined as the sum of all the physical factors (irradiation, direct conduction, and convection) that contribute to the transmission of caloric energy from the environment to the body. Humidity increases the specific caloric load per volume of air and interferes with the cooling capacity of the organism by means of evaporation through perspiration (2). In the climatic conditions just described, there is almost no temperature difference between the body and the environment, and the body cannot disperse the excess thermal energy created by metabolic and motor activities.

Neuroleptic malignant syndrome is a rare and severe complication of neuroleptic treatment characterized by hyperthermia, muscular rigidity, and autonomic dysregulation. Neuroleptic malignant syndrome is observed in 0.5% of all treatment episodes and has a mortality rate of 15%–22% (1, 3). The reasons for the occurrence of the syndrome at a particular moment in the patient's drug treatment history are not clear. Neither the patient's characteristics (such as age, diagnosis, concurrent medical illness) nor those of the drug are sufficient conditions: neuroleptic malignant syndrome has occurred in patients who had been safely treated with the same drug on previous occasions and in others who were safely rechallenged with the same drug immediately after neuroleptic malignant syndrome (1, 3). The occurrence of the syndrome depends, therefore, on the concurrent presence of multiple factors.

Contributing factors such as a rapid increase in dose (1), agitation, and physical exhaustion (4) have been advanced. Other authors (5, 6) have questioned the role of ambient heat as a triggering factor. Definite endorsement of such a claim is difficult: climatic conditions associated with neuroleptic malignant syndrome are inconsistently reported. Data concerning the season in which the syndrome occurred (which could provide an indirect indication of the associated climatic conditions) were found in only 34 (28%) of 120 case reports cited in a previous review (1) (19 cases occurred in the winter and 15 occurred during the summer). Such information is, however, of limited value considering the fact that psychiatric wards are often overheated during the winter. Similarly, in a recent review (7), dehydration was associated with neuroleptic malignant syndrome in seven of 39 patients, but it is again difficult to evaluate whether dehydration was secondary or was one of the triggering factors.

In the three cases presented here, neuroleptic malignant syndrome developed during extreme weather, in hospital rooms without air conditioning, and heat load could have been a contributing factor.

CASE REPORTS

Case 1. Mr. A, a 24-year-old man with bipolar affective disorder, was admitted in August for mania with mood-congruent delusions. The weather was hot and humid; the temperature ranged from 30°C to 36°C (86°F to 97°F), and the humidity exceeded 70%. On admission, he was physically fit, and the results of laboratory screening were normal.

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He began treatment with 5 mg t.i.d. of intramuscular haloperidol. On the third day of treatment he developed a fever (39.5°C, or 103.1°F), tachycardia, diaphoresis, and marked muscular rigidity. Haloperidol administration was discontinued, but Mr. A became stuporous and dysphagic. His creatine phosphokinase level rose to 3200 IU/liter, and he developed an elevated SGOT level (189 IU/liter) and leucocytosis. Concurrent infection was excluded. Treatment with amantadine, 300 mg/day, and dantrolene, 200 mg/day, resulted in a progressive alleviation of symptoms. Mr. A became alert and euthermic in 6 days.

Case 2. Mr. B, a 27-year-old schizophrenic man, was admitted during the same heat wave of August with marked agitation and disorganized and bizarre paranoid delusions. The results of physical and laboratory examinations on admission were negative. He was started on a regimen of 300 mg/day of chlorpromazine and on the third day of treatment developed neuroleptic malignant syndrome characterized by hyperthermia (39.1°C, or 102.4°F), diaphoresis, marked cogwheel rigidity, and somnolence. He had a maximum creatine phosphokinase level of 2200 IU/liter, an SGOT level of 88 IU/liter, and a WBC of 13,700 cells/mm^3. Neuroleptic treatment was stopped, and conservative treatment was implemented. All signs of neuroleptic malignant syndrome disappeared within 8 days.

Case 3. Mr. C, a 63-year-old man with bipolar affective disorder, was admitted in July for a manic episode after the administration of antidepressants. Treatment began with perphenazine, and the dose reached 16 mg/day within 2 days. Twenty-four hours later he became diaphoretic and complained of difficulties in swallowing. The external temperature that day was 30°C to 34°C (86°F to 93°F), and the humidity exceeded 60%. Twelve hours later, he became febrile (38.7°C, or 101.7°F) and disoriented. A neurological examination revealed marked muscular hypertonia and coarse tremor. Perphenazine treatment was stopped, but Mr. C's condition deteriorated. He was transferred to an intensive care unit, where, in spite of intensive treatment (including symptomatic measures and administration of dantrolene and bromocriptine), he developed severe hyperpyrexia (42.1°C, or 107.8°F), an extremely high level of creatine phosphokinase (65,000 IU/liter), myoglobinemia, and finally, pneumonia with a fatal outcome.

DISCUSSION

Neuroleptics were originally developed and investigated for their effect on thermoregulation during "artificial hybernation." They were found to have a complex effect on thermoregulation, resulting in phenomena such as heat stroke (8) and neuroleptic malignant syndrome. Neuroleptics were shown to reduce the body's resistance to both heat load and cooling; reduction of the body's resistance to cooling is regularly observed in humans (e.g., in the external cooling of hyperthermic patients, phenothiazines are useful for reducing shivering) (2). Decreased resistance to heat load in humans has been documented in vitro (9) and in vivo (8).

Several mechanisms have been proposed to account for these effects, among them 1) direct action on hypothalamic thermoregulatory mechanisms, resulting in derangement of central thermoregulation, and 2) an anticholinergic effect, which interferes with sweating and reduces the capacity for cooling by evaporation.

The pathophysiology of hyperthermia in neuroleptic malignant syndrome is unknown. The two explanatory models are 1) a central dopamine receptor blockade resulting in a derangement of thermoregulation and 2) peripheral hypermetabolic state due to a direct effect of neuroleptics on skeletal muscle tissue resulting in excessive heat production. Mills and Robertshaw (10) found that plasma prolactin levels increased during heat load. This effect was apparently mediated by a neuronal chain starting at the thermosensitive site at the preoptic area and involving an inhibition of the dopaminergic terminals responsible for the tonic inhibition of prolactin release in the median eminence. Such a pathway could explain how heat load could trigger neuroleptic malignant syndrome in the context of a massive down-regulation of dopamine receptors due to neuroleptic administration. Once triggered, both central and peripheral mechanisms would play a concurrent role.

Considering the high rate of mortality from neuroleptic malignant syndrome, its triggering factors are of central interest. Our observations suggest that adverse climatic conditions (including microclimate, such as overheated hospitals) should be considered by clinicians as a potential cofactor in neuroleptic malignant syndrome.

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The Homeless Mentally Ill in Tucson: Implications of Early Findings

Leona L. Bachrach, Ph.D., Jose M. Santiago, M.D.,
Michael R. Berren, Ph.D., and Mo Therese Hannah, M.C.

Homeless persons who received emergency psychiatric screening in a public general hospital exhibited patterns of gross geographic mobility. They did not uniformly avail themselves of community services, such as soup kitchens, and there were marked sex differences within the sample.

(Am J Psychiatry 1988: 145:112–113)

The Tucson Homeless Mentally Ill Study was designed to increase understanding of homeless individuals receiving emergency psychiatric services at a public general hospital. This article reports on the first wave of data collection from that study.

Kino Community Hospital serves Pima County, Arizona, and is virtually the only facility in a community of 500,000 individuals that provides emergency and inpatient psychiatric care to the indigent chronically mentally ill of greater Tucson (1). Begun in October 1986, the study compares domiciled and undomiciled emergency room patients referred for psychiatric screening across an array of demographic and treatment variables. Although other studies of the homeless of Tucson have been conducted (2–5), the Tucson Homeless Mentally Ill Study is the first to focus on a hospital-based sample. It has been noted that homeless mentally ill individuals who use general hospital psychiatric services probably constitute a distinctive grouping within the total population of homeless mentally ill individuals (6, 7).

METHOD

All patients seen during the daytime and evening shifts in the emergency room at Kino Community Hospital from October 1986 through February 1987 and referred for psychiatric screening by the emergency services physician were eligible for inclusion in the study. Data collection was randomized according to the time of day, so that all individuals screened between the hours of 8:00 a.m. and 10:00 p.m., Monday through Saturday, had an equal chance of being included.

Patients were asked if they would spend 15 minutes with an interviewer to discuss housing and other problems. Those admitted to the psychiatric inpatient unit were interviewed after their admission, usually within 24 hours; those not admitted to inpatient care were interviewed before their release from the emergency service. Only three patients who were invited to participate refused.

All interviews were conducted by trained interviewers employed as research assistants in the hospital's department of psychiatry. The research instrument was designed specifically for this study and had been used in a pilot study of 185 patients during August and September 1986.

RESULTS

Of 264 individuals who received emergency psychiatric screening at Kino Community Hospital, 41 (16%) were homeless (i.e., they were living on the streets, in automobiles, or in shelters or missions) at the time of their emergency room contact. The median age of this group was 32 years, and over three-fifths (63%) were male. The 223 domiciled individuals (84%) who received emergency psychiatric screening during the same period also had a median age of 32 years but were more evenly distributed by sex (49% male). A strikingly smaller percentage of the homeless individuals (54%) than of the domiciled individuals (73%) were admitted to the hospital's 36-bed psychiatric inpatient unit.

Although the small number of cases does not permit extensive comparisons within the homeless group, some suggestive findings emerged from the first wave of data collection in this study. Of particular interest is homeless individuals' residence at the time of the emergency room contact. Of the 26 men, 81% lived on the streets, 11% in shelters or missions, and 8% in

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automobiles. The respective percentages for the 15 homeless women were 47%, 33%, and 20%.

Also of interest is the fact that most of the homeless patients were recent arrivals in the community. The median duration of residence in Pima County for the homeless men was 5 months, and that for the homeless women was less than 1 month. By contrast, the domiciled women showed a substantially longer median duration of residence in the county than the domiciled men: 95 months and 54 months, respectively.

Pima County provides a number of soup kitchens where homeless individuals may receive their meals. The study revealed that 70% of the homeless men and 77% of the homeless women who received emergency psychiatric screening reported using those soup kitchens; the remaining homeless individuals apparently received food from other sources. It is also interesting to note that 13% of the 109 domiciled men and 12% of the 114 domiciled women reported using soup kitchens as a source of food.

DISCUSSION

The small numbers of patients included in this wave of data collection limit the generalizability of the results. In addition, some bias is introduced by the fact that the sample excluded late night and Sunday screenings, although administrative records in the department of psychiatry reveal that 93% of all emergency psychiatric screenings occur during the daytime and evening shifts.

Nonetheless, the data contain some important implications for future research. This study provides evidence that gross geographic mobility—a circumstance widely presumed to exist among the homeless, but poorly documented (6)—indeed characterizes some homeless mentally ill groups. Whether such mobility is associated with utilization of general hospital emergency psychiatric units remains to be tested in other study sites.

The study results further underscore the difficulties associated with generalizing from facility-based homeless populations. Specifically, although counts of individuals who receive food in soup kitchens are sometimes used to approximate the homeless population (2–4, 8), the study data clearly indicate that not all homeless mentally ill individuals use those facilities. Moreover, some soup kitchen patrons who are mentally ill are not homeless, and caution must be exercised in generalizing from data gathered in those facilities.

Finally, sex differences among the homeless mentally ill must be explored if appropriate services are to be designed for and offered to this population (9). The remarkably brief duration of residence in Pima County of homeless women, the greater frequency of their residing in shelters and automobiles, and their greater dependence on soup kitchens point to the need for specific planning considerations for both men and women.

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Rapid Cycling Bipolar II Illness in Three Closely Related Individuals

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The author describes three related women with rapid cycling bipolar II disorder. Their cycles of approximately 55 days usually included 3–7 days of hypomania, followed by 5 weeks of mild to moderate depression and 2 weeks of severe depression.

(Am J Psychiatry 1988; 145:114–115)

The inheritance of bipolar disorders has been described in many studies (1, 2). However, it has been difficult to demonstrate that specific characteristics of bipolar illness may be inherited independently.

Dunner et al. (3) used the term "rapid cycling bipolar illness" to describe disorders in which there were four or more episodes of affective illness in 1 year. In studying family histories of bipolar patients, with or without rapid cycling, Dunner (4) was not able to demonstrate that rapid cycling was inherited independently of other characteristics of bipolar disorder.

Fieve and Dunner (5) distinguished between bipolar I disorders, in which there were classic manic episodes requiring hospitalization, and bipolar II disorders, in which there were brief, relatively mild hypomanic episodes not requiring hospitalization. Subsequent studies (1, 6, 7) have demonstrated that bipolar II individuals are more likely to have relatives with bipolar II disorder than with bipolar I disorder. In this paper we describe three relatives who had rapid cycling bipolar II disorder.

CASE REPORTS

Case 1. Ms. A had been an unhappy, fearful child. Her first psychiatric hospitalization occurred after a suicide attempt at the age of 17. After her second hospitalization, for severe depression, at the age of 28, her social functioning gradually deteriorated. From age 33 to 38, she had six psychiatric hospitalizations; her symptoms included suicidal ideation, agitation, anxiety, suspiciousness, depersonalization, low self-esteem, and dependency.

Ms. A was 38 years old when I first saw her. Her main complaints were of depressed mood and difficulty sleeping. During detailed questioning, she said she had periods of euphoria lasting about 4 days.

During the first 4 months of treatment, she had two brief episodes of euphoria. She was treated with lithium carbonate, 1200 mg/day; her blood level was 0.9–1.2 meq/liter. Euphoric episodes did not occur during the 20 months she received this treatment.

She continued to have depressive symptoms, including preoccupation with suicide, feelings of guilt, lack of energy, sleep disturbances, vague visual hallucinations, and auditory hallucinations, usually a voice calling her name.

After Ms. A had been taking lithium carbonate for about 20 months, it was discontinued because of a medical problem. It was resumed at a dose of 600 mg/day, after which her lithium blood level reached 0.6–0.8 meq/liter. During the next 3 years and 9 months, she had 17 episodes of euphoria. The intervals between euphoric episodes were either 50–60 days or approximate multiples of these numbers. During the periods of euphoria, which lasted 3–7 days, she was silly and jovial, talked rapidly, and was more active than usual. She often had racing thoughts and difficulty sleeping. Between the periods of euphoria, there were periods of euthymia and depression. The depression was most severe during the 2 weeks before the switch to euphoria.

Case 2. Ms. B, the niece of Ms. A, reported having no emotional problems as a young child. At the age of 15, after smoking what she thought was marijuana she had an episode of anxiety, confusion, and visual hallucinations and required psychiatric hospitalization. After that, she did not use illicit drugs.

After 4 years of good functioning, she had an episode of depressive symptoms, which she described as distinctly different from her previous symptoms. Her symptoms also included anxiety, panic, depersonalization, and obsessional and narcissistic symptoms. After this episode, she continued to have anxiety and difficulty sleeping. She was unable to keep a job longer than a month.

Ms. B was 22 years old when I first saw her. She had numerous complaints, including anxiety, difficulty with her memory, menstrual irregularities, abdominal pain, and mild depression. During the period of observation, it was noted that her symptoms occurred primarily when she was depressed. She refused medication.

During a period of 3 years and 7 months, she had 17 episodes of euphoria, lasting 3–7 days. The intervals between episodes were either 50–60 days or approximate multiples of these numbers.

When Ms. B was euphoric, she was very active and had rapid speech. She was unrealistically confident and often

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spent money impulsively. She reported racing thoughts and an increased amount of energy.

Ms. B's depressive symptoms were most severe during the 2 weeks before the onset of euphoria. When depressed, she had decreased energy, difficulty sleeping, and a loss of interest in her usual activities. She occasionally had suicidal thoughts and vague visual hallucinations but no auditory hallucinations.

Case 3. Ms. C, the sister of Ms. A and mother of Ms. B, reported having had suicidal thoughts at the age of 11 and having been depressed frequently since then. She had avoided psychiatric treatment except for a brief hospitalization for depression at the age of 40. Although she denied that she had ever been unusually happy, her sister and daughter (Ms. A and Ms. B) reported that she was often jovial, energetic, and irritable.

Ms. C was 46 years old when I first saw her. During the period of observation, she was taking imipramine; her dose ranged from 50 to 200 mg/day, depending on her mood.

About 6 weeks after she was first seen, Ms. C was noted by others to be jovial and irritable. She did not report feeling unusually happy but did report an increase in energy. Over a period of 1 year and 8 months, there were nine similar periods of irritability, increased energy, and rapid speech, which lasted 2–4 days. The number of days in each interval was either 55–60 or 106–110. Ms. C also had depressions, which were more severe during the 2–3 weeks before the periods of euphoria. When depressed, she had decreased energy, loss of interest in her usual activities, low self-esteem, and difficulty concentrating. She often slept during the day.

DISCUSSION

These individuals had mood cycles, with periods of euphoria at intervals of about 55 days. Each of them had symptoms that were consistent with the Research Diagnostic Criteria (8) for bipolar disorder with hypomania, which is equivalent to the diagnosis of bipolar II disorder. The pattern of their cycles is similar to patterns described by Himmelhoch et al. (9) and Kukopulos et al. (10). Confirming the existence of this syndrome would depend on data derived from carefully documented, prospective investigation, including epidemiological, genetic, and physiological studies.

Rapid cycling bipolar illness has been considered to be a relatively rare condition that is seen in large numbers of patients only in research centers (3, 9). However, it is possible that rapid cycling bipolar II illness is an inherited condition which is underdiagnosed. Ms. B and Ms. C denied many of their symptoms in giving their initial histories. The diagnosis of rapid cycling bipolar II illness was made only after careful documentation of mood changes. Any patient with a confusing history including some depression should be followed over a period of time, and an attempt should be made to document mood cycles, especially if the patient has a relative with rapid cycling affective illness.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

CLINICAL ISSUES

Psychiatry Update: American Psychiatric Association Annual Review, vol. 6, *edited by Robert E. Hales, M.D., and Allen J. Frances, M.D. Washington, D.C., American Psychiatric Press, 1987, 825 pp., $49.95; $36.95(paper).*

A hybrid of a textbook and a scientific journal, the *American Psychiatric Association Annual Review* now flourishes in its sixth season. And what a robust and hardy perennial this series has become—a veritable living litmus of the fertility and vitality of our field. This year, one in five APA members will purchase a copy of this *Update,* and they will be treated to a bouquet of timely clinical and basic science presentations.

The remarkable success and value of the *Update* series are rooted in its workable concept and the unparalleled accomplishment of its editors, now Robert Hales and Allen Frances, who yearly select five important topics and recruit section editors and authors to explore these topics in depth. The *Update* is tightly edited to avoid redundancy and is unified by the editorial instructions to be clinically relevant, to be data based, and to place special emphasis on the important new ideas in each area. Remarkably, the time from the selection of topics and section editors to the publication of the *Update* is approximately 18 months. This time frame rivals and often eclipses the time from submission to publication of articles in even the most efficient scientific journals and ensures the inclusion in the *Update* of new clinical approaches as well as fresh research data.

Volume 6 of the *American Psychiatric Association Annual Review* has adhered to and further refined the vital *Update* concept. Each of the 26 chapters is a valuable contribution and merits individual notation and praise, but this, manifestly, is beyond the structural constraints of a book review. Of necessity, therefore, I will stroll through this garden of delights to pluck a specimen or two from each section in an effort to reflect the vast appeal of the whole.

Considered in the section entitled Bipolar Disorders, edited by Frederick K. Goodwin and Kay Jamison, are differential diagnosis, natural course, and epidemiology; biological findings; sleep and biological rhythms; treatment; psychotherapeutic issues and suicide prevention; and treatment-resistant bipolar illness. Required reading for the practicing clinician is Goodwin and Peter P. Roy-Byrne's chapter on pharmacologic treatment (e.g., lithium doses, blood levels, clinical monitoring for side effects, and management of "breakthrough" manias and depression) and Post and Uhde's chapter on pharmacologic treatment of patients with lithium-resistant bipolar illness. Topical, comprehensive, and well presented are the data on use of valproic acid and other agents reported to be effective. Never was the term "update" more appropriately applied than in this section on bipolar illness.

Current and relevant information is presented in the section on Neuroscience Techniques in Clinical Psychiatry, edited by John M. Morihisa and Solomon H. Snyder. Included in this section are pharmacology, endocrinology, and psychoimmunology in clinical psychiatry as well as basic concepts and clinical implications of the neurobiology of sleep, CAT scanning, magnetic resonance imaging, and functional brain imaging (e.g., positron emission tomography, computerized EEG and evoked potential mapping, single photon emission computerized tomography, and regional cerebral blood flow). Such issues as the "two-disease theory of depression" (i.e., catecholamine and indoleamine) and the value of blood level measurements of antipsychotic medications are critically and lucidly reviewed. A welcome feature of this section is that, after divergent theoretical data are presented, the authors often take stands as to which approach or conclusion they feel most likely to be correct. The chapters on psychoendocrinology and psychoimmunology in clinical psychiatry, which include, for example, a discussion of the neuroendocrine and neurotransmitter regulation of immune function, are fascinating and have almost unfathomable implications for future discovery. The chapters on the neurobiology of sleep and imaging in psychiatry are written by authors who have made seminal contributions in these areas; in my opinion, these are among the best and most current available overviews of these topics.

The section entitled Differential Therapeutics, edited by John F. Clarkin and Samuel W. Perry, is organized according to five major decisions that the clinician must make in formulating a treatment plan: the setting for treatment (inpatient, outpatient, day hospital), the format of treatment (individual, group, family), strategies and techniques of treatment (exploratory, cognitive, behavioral), the frequency and duration of treatment, and the choice of medication. Perry has written two ground-breaking books on differential therapeutics (1, 2), one with Allen Frances (1). He and Clarkin define the goal of this section of the *Update* as providing a clear statement of what we know and what still remains to be learned about treatment selection. Carl Salzman and Alan I. Green's chapter on psychopharmacology explores such important and elusive issues as delusional depression, lithium-resistant affective disorder, and the strategy for low-dose management of acute behavioral disruption and schizophrenia. The authors encourage the reader to avoid such treatment clichés as assuming that a 4-week course of at least 300 mg of imipramine (or the equivalent) constitutes an adequate therapeutic trial for most depressions; recent data suggest that an adequate trial would be 6 weeks of treatment at high-dose levels. An important clinical point that was not included here is the misuse of antipsychotics in the "treatment" of agitation and aggression related to chronic brain syndromes. β Blockers and anticonvulsants are safer and more effective choices in such cases. Perry's chapter is intriguing and iconoclastic. He challenges the data and reasoning behind the conventional frequency and duration of psychotherapy sessions. He discusses the value of consultation without further treatment and even the occasional recommendation of no treatment as a specific therapeutic intervention.

The section on Violence and the Violent Patient, edited by

Kenneth Tardiff, encompasses determinants and sociological patterns of human violence, clinical evaluation of the violent patient, emergency management and long-term treatment of the violent patient, and legal aspects of violence by psychiatric patients. Park Elliott Dietz's consideration of patterns of human violence is as intriguing as it is unsettling. This chapter unearths a treasure trove of statistics that the author synthesizes and integrates into revealing, memorable, and useful information. Particularly enlightening is the discussion of the characteristics of both offenders and victims involved in attacks, robberies, and homicides. Paul S. Appelbaum's chapter on the legal aspects of violence by psychiatric patients expertly dissects and delineates the legal demands placed on psychiatrists with regard to the control of violent patients. He states, "Society now expects clinicians effectively to control their patients' violent proclivities and threatens liability if clinicians' efforts are unsuccessful" (p. 562). However, the tools available for this purpose (e.g., the involuntary administration of medications, seclusion and restraint, and involuntary hospitalization or outpatient treatment) are themselves limited by regulations that seek to promote other ends which society deems important. All practicing psychiatrists must be familiar with the intricacies inherent in fulfilling these legal obligations as they relate to the violent patient or be vulnerable to legal consequences of acting imprecisely (such as incorrectly assuming that it is legal to administer medication involuntarily to a patient who has been legally committed to inpatient hospitalization). Appelbaum's chapter portrays these conflicting and often irreconcilable legal constraints with precision and clarity.

Myrna M. Weissman, editor of the section on Psychiatric Epidemiology, documents that psychiatric epidemiology in the United States is undergoing a major and important shift from the study of the prevalence of general psychiatric impairment to the study of the prevalence and incidence of specific psychiatric disorders. The goal of this section is to acquaint the psychiatric clinician with a variety of epidemiologic approaches that are currently yielding important data for the clinician. Included among the chapters are such gems as "Genetic Epidemiology of Psychiatric Disorders," "Parental Mental Disorder as a Psychiatric Risk Factor," and "Toward the Prevention of Psychiatric Disorders." An unexpected surprise was the chapter "Epidemiologic Findings From Disaster Research," which considers floods, volcano eruptions, nuclear accidents, riots, and other human catastrophes. Lifetime prevalence rates of major depression and drug abuse are also explored in depth in this section.

The final section of volume 6 of the *Annual Review* focuses on Psychopharmacology: Drug Side Effects and Interactions. Edited by Leo E. Hollister and Philip A. Berger, this section is straightforward, interesting, and practical. Individual chapters consider side effects of antipsychotics, antidepressants, lithium carbonate and carbamazepine, benzodiazepines, and clinically significant psychoactive drug interactions. For example, the reader can find out what is the proper response if a psychotic patient develops cholestatic hepatic toxicity when given one class of phenothiazines or what are the preferred treatments of such common antipsychotic side effects as akathisia, parkinsonism, tardive dyskinesia, tardive dystonia, and extrapyramidal symptoms and fever. Jefferson and Greist's chapter on the side effects of lithium carbonate and carbamazepine is masterful and comprehensive. Such rarely considered issues as the effects of lithium on creativity, neuromuscular systems, and sleep and lithium's association with tardive dyskinesia and pseudotumor cerebri are discussed, along with the more common endocrine, immunologic, cardiovascular, gastrointestinal, renal, reproductive, and dermatologic side effects. For me, this chapter alone was worth the price of the entire book. Clinically significant psychoactive drug interactions that may enhance therapy, decrease the desired efficacy of a medication, or produce unwanted side effects are explored in a chapter by Csernansky and Whiteford. The authors make excellent use of six tables that clearly depict the interacting compounds and the clinical outcomes of such interactions. Unfortunately, the prose accompanying the excellent tables is skimpy and incomplete. For example, the role of lithium or T_3 in enhancing the antidepressant effects of tricyclics is not addressed, nor is the danger of combining thioridazine with propranolol, which can result in two to three times the expected plasma levels of thioridazine.

Similar omissions and the occasional failure of an author to amplify sufficiently on a topic represent my major criticism of the *Annual Review*. For example, in the otherwise excellent chapter on sleep and biological rhythms in bipolar illness, the authors, leading authorities on the use of phototherapy in the treatment of seasonal affective disorder, fail to delineate fully their preferred protocols for phototherapy of bipolar illness. In this case and that of most other omissions in the *Update*, the interested reader may easily use the accompanying references to locate additional information.

In conclusion, the *American Psychiatric Association Annual Review* has become the most efficient and stimulating way for the psychiatrist to maintain his or her knowledge of the field. Useful, entertaining, inspiring, and a source of pride for all psychiatrists, volume 6 of the *Annual Review* is the best answer to the question, What's new in psychiatry?

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The Perspectives of Psychiatry, revised and expanded ed., *by Paul R. McHugh, M.D., and Phillip R. Slavney, M.D. Baltimore, Johns Hopkins University Press, 1986, 162 pp., $8.95 (paper).*

This is a wonderful little book: exciting, stimulating, and provocative. As I read it, I kept thinking how much it could have helped 20 years ago in the bad old antipsychiatry days, when the "myth of mental illness" was so popular and the notion of psychiatry as conspiracy was riding high. McHugh and Slavney's ideas are just as valuable today in confronting the excesses of a mindless psychiatry that sees panaceas in each new biological advance.

The authors locate the source of the recurring difficulties that beset our field in the mind-body problem: "Synthetic explanations from the molecule up and reductionistic explanations from the thought down do not meet, but leave a gap so wide that the most obvious feature of mental life—its subjective sense of purposiveness and meaning—remains disconnected from the objectively demonstrated dependence of that life on neurological integrity." No similar disjunction occurs in other branches of medicine. Unique among fields of medicine, psychiatry may choose to include the mind within its domain, which results in problems as well as unbounded opportunity.

The authors recognize at the outset that the disjunction between body and mind cannot be bridged and that understanding the two worlds of form and function requires two very different ways of knowing. One way of knowing is that associated with the natural sciences, "the knowledge of forms appearing among other forms and differentiated by their characteristics, frequency, temporal appearance, and association." The other way of knowing, what the Germans discriminate from natural science as *Geisteswissenschaften,* is the knowledge of the "functions" of a person that reveal the goals and meanings of his or her life. "This way of knowing is different from that in which one knows a fact, such as the square root of 25; rather, it is the sense in which we know what it feels like to be intimidated, powerful, frightened, or in love."

The difference between the two ways of knowing goes beyond differences in the ways they are experienced. They are, for example, "not derived from different interpretations of experimental results based on a shared paradigm. Rather, they are two different conceptions of the field, with different standards, operations, and paradigms. . . . Kraepelin is not refuted by Freud, nor do Freudians feel confounded by data from psychopharmacology." The authors refer to this conflict between the two ways of knowing as dialectical—a dialectic confined to thesis and antithesis, with no synthesis in sight: "The problem of the psychiatrist is that it is difficult, if not impossible, to view a mental disorder in these ways simultaneously. Parallax occurs, so that mental features seen as forms from one vantage point are regarded as functions from another." The care of the patient thus requires a constant shifting of the vantage point of the psychiatrist from that of form to that of function and back again.

Having established the nature of this dialectic, the authors turn to the four perspectives of their title—four approaches to classification, understanding, and treatment. These perspectives—disease, dimensions, behaviors, and the life story—have little in common and represent radically different conceptual approaches. There appears to be a progression in the perspectives from those which are the most congenial to an analysis of form to those which conform better to an analysis of function, although the authors do not treat this issue. Thus, the first perspective, that of disease, is admirably suited to an analysis of form, and the authors present a masterful discussion of disease (and, incidentally, of the much maligned medical model), showing its elegance and power in the understanding of such diseases as dementia and delirium and of such candidates-to-become-diseases as schizophrenia and manic-depressive illness. In coping with disease, the psychiatrist may operate in a manner indistinguishable from that of other physicians. Not so in coping with disorders delineated by the other three perspectives.

The authors discuss in a cogent and lucid manner the perspectives of dimensions and behaviors. But it is in their treatment of the fourth perspective—the life story—that their analysis of function reaches its apogee. The argument begins with a consideration of the self, "the sense of the person as director or pilot of his life," and "the intentions of the self and their consequences in relation to other intentions, emotions, and behaviors." It goes on to assert that "there are consequences to certain intentions that are unwanted, unsought, and distressing" and that much of psychotherapy is designed to show "how unintended consequences emerge from intentional actions. . . . If the self, its intentions, and their consequences are the ingredients of a meaningful psychiatry, the method we are here calling life story reasoning is what gives them the power of conviction—the sense of knowing that is both illuminating and irresistible."

The life story is the view that a person has of himself or herself, a view which becomes the central focus of psychotherapy as patient and therapist work together to create a new life story that provides the rationale for changing the patient's future. Thus, although psychotherapy may appear to be many things, it is basically a means of persuasion. Unlike other therapies, psychotherapy does not "seek to interrupt a process of a specific character that has a predictable course. It is an effort to help a person choose to live more successfully in the present and to confront any future more effectively. Its aim is a person perfected. . .rather than a disease cured."

The authors further point out that

> the ability to construct the best story for a particular patient depends upon imaginative reconstruction of his past experiences. The type of understanding that emerges is similar to that of historians and is indispensable. It brings an understanding of patients as individuals with a story to tell rather than an impairment to explain. It helps us to see that man is both determined by his past and free to change his future, and that, sane or mad, he lives his life in a world filled with meaning.

All of this rich fare is encompassed in prose that, as the many quotations indicate, I found particularly felicitous. I predict for this small volume a long life and a profound influence on our field.

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The Patient: Biological, Psychological, and Social Dimensions of Medical Practice, 2nd ed., *by Hoyle Leigh, M.D., and Morton F. Reiser, M.D. New York, Plenum, 1985, 457 pp., $29.50.*

In the preface to the first edition of this book (1980), the authors extended to their readers the courtesy of saying what the book was not: "This book is *not* a conventional textbook of behavioral science. This book is *not* a conventional textbook of medicine. This book is *not* an introduction to clinical psychiatry." The grateful reader was thus forewarned about what not to expect and was therefore very pleasantly surprised to discover what the first edition was: a serious and largely successful integration of the behavioral sciences with the biological, psychological, and sociocultural perspectives of both medical and psychiatric practice. The organizing theoretical principle throughout the first edition was the general systems approach. My admiration of the first edition of this book now extends to this second edition.

The second edition is essentially the same book but with expansions in a number of areas. Part one, On Becoming a Patient, again describes illness and help-seeking behavior, the sick role, and expectations in the consulting room. In part two, On Being a Patient, we again have the superb chapters on anxiety, defense mechanisms, depression, pain, and sleep, but now there are two important additional chapters on psychosis and organic brain syndromes. It is in part three, On Assessing a Patient, where we find the unique contribution of the Patient Evaluation Grid (PEG), which has been revised and further systematized from the three-by-three grid that was presented in the first edition. This grid allows the clinician to conceptualize the intersection of data from three dimensions of organization (biological, psychological or personal, and environmental or sociocultural) with three time contexts (current, recent, and background). In the second edition, a companion grid is offered—the PEG-Management Form—which provides three-dimensional diagnosis as well as treatment management plans for the patient. Part four, On Managing a Patient, once again focuses on the doctor-patient relationship, including descriptions of personality types often seen among patients, several fascinating and poignant illustrative case histories, and therapeutic approaches to patients conceptualized along the biological, psychological, and sociocultural dimensions.

When George Engel first introduced the concept of the biopsychosocial model in 1977, it was clear that he had captured the essence of not only modern psychiatry but all of modern medicine as well. The earlier biomedical model was simply no longer sufficient for either good medical or good psychiatric care, if indeed it ever was sufficient. For every patient, the diagnostic evaluation must include consideration of biological, psychological, and sociocultural descriptive data, and the therapeutic approach must integrate biological, psychological, and sociocultural therapies. Very few books make the biopsychosocial model for both diagnosis and treatment come as alive and vivid as this book does.

From a more personal perspective, both the first and second editions have contributed substantially to my own thinking as a clinician and as an educator and have helped me to integrate many aspects of the behavioral sciences into my clinical work. *The Patient* also prompted me to think about developing my own "grid." It is also a three-by-three grid, with biological, psychological, and sociocultural dimensions on the vertical axis, but rather than time contexts on the horizontal axis, I have placed descriptive, dynamic, and developmental-genetic dimensions instead. The descriptive dimension asks what symptoms or syndromes currently exist from data obtained through the physical examination (biological), the mental status examination (psychological), and the examination of the current life setting (sociocultural). It thereby incorporates the current time context of Leigh and Reiser in a way that I hope more clearly emphasizes the descriptive contributions of current psychiatric nosology as exemplified by *DSM-III* and *DSM-III-R*. Recognizing that nosology as essentially limited to description, however, I think it is imperative to have an etiological perspective in our evaluation of patients as well. The dynamic dimension attempts to explain how a given symptom or syndrome has come about through the current or recent interaction of multiple biological, psychological, and sociocultural etiologies, and the developmental-genetic dimension attempts to explain why a given symptom or syndrome has come about through the past (or background) interaction of nature (genetic and other constitutional factors) and nurture (developmental factors and environmental experiences). That happens to be my patient grid. Others will develop their own grids for patient evaluation and therapeutic management. What we all have in common is a debt to the creative scientific and educational contributions of Hoyle Leigh and Morton F. Reiser.

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Making Sense of Psychiatric Cases, *by Maurice Greenberg, George Szmukler, and Digby Tantam. New York, Oxford University Press, 1986, 256 pp., $17.95 (paper).*

Drs. Greenberg, Szmukler, and Tantam have written a psychiatric casebook aimed at teaching the skills of ordering clinical data in a way that makes the formulation of the case the source of the patient's treatment plan. Their work is intended for medical students, psychiatric residents, and others in need of an introduction to the process of clinical formulation.

In my own psychiatric training the teaching and learning about clinical formulation were not clearly focused. In the first year trainees were confronted with the task of writing a patient's "anamnesis"—a document distinguished primarily by its length. In the following years case formulations emerged through clinical supervision in which the value attached to learning the process of formulation depended on the priorities of the supervisor. Therefore, learning how to construct and use a clinical formulation was a somewhat haphazard enterprise. Because I expect that my experience is shared by others, *Making Sense of Psychiatric Cases* addresses an important and often neglected aspect of psychiatric education.

The authors base their 12 case presentations on a biopsychosocial model of understanding psychiatric problems and on an appreciation of the unique context of the patient's own particular life circumstances. Most of the cases are representative of those seen in the practice of general psychiatry, and there is some bias toward problems of consultation-liaison and inpatient care. The format used for case formulations encompasses the diagnosis, symptoms supporting the diagnosis, and the etiology of the problem, which is further subdivided into biological and psychosocial components, each having a predisposing, provoking, and exacerbating dimension.

The authors correctly point out that this method of organizing the data allows one to integrate issues from different conceptual domains. What is not sufficiently emphasized is that it requires experience, skill, and good judgment on the part of the clinician to determine which issues within the formulation must take priority. In tone and feeling these cases seem a little distant from actual clinical interactions with patients. They remind one of the case histories presented at a clinical pathological conference. This distance is useful in allowing the reader the opportunity to construct alternative formulations and treatment plans based on the available data, an exercise the authors suggest. Since many cases are presented longitudinally, follow-up data and reformulations are often given.

This book comes from the tradition of psychiatric practice in Great Britain. For me one of its principal pleasures was getting a sense of the experience of psychiatric patients in that system of health care. For readers in the United States, however, there are no references to *DSM-III* and some psychotropic medications mentioned in the text may be unfamiliar. The book discusses its philosophical premises only in a brief postscript. I feel the omission of a more complete discussion is a mistake in a volume intended as an introductory work. I also object to the absence of references. Since there are no timeless formulations—only timely ones—the authors would have done well to include some basic references on which their formulations are grounded. Just as a patient's symptoms exist within the context of a specific life history, so too does the psychiatrist's thinking exist within a scientific and clinical body of knowledge.

Making Sense of Psychiatric Cases uses the case study method to illustrate the value of systematic data gathering and careful clinical formulation. The book is elegant in its conception but in a curious way is a little too removed from other important clinical concerns—such as the skills connected with clinical interviewing, differential diagnosis, and constructing treatment interventions. Therefore, this book can best be used as a teaching guide in conjunction with clinical seminars or with other suitable and complementary clinical texts.

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ETHNIC PSYCHIATRY

Ethnic Psychiatry, *edited by Charles B. Wilkinson, M.D. New York, Plenum, 1986, 199 pp., $25.00.*

This book has a very laudatory foreword by Shervert Frazier, former Director of the National Institute of Mental Health (NIMH). Dr. Frazier enunciates the goals of the book as 1) to stimulate awareness about the ethnic groups discussed in the book, 2) to reinforce knowledge about different cultures, and 3) to provide a valuable clinical tool for the practitioner.

The body of the book comprises an introductory chapter and four chapters dealing with the basic minority groups of the United States: blacks, Hispanics, Asians, and Native Americans.

The introductory chapter offers a good explanation of the focus of the book. Ethnicity, social class, race, and minority status are well differentiated. The chapter on blacks is well written and well conceptualized. The focus in this chapter on oppression, discrimination, and racism is related well to the objectives of the book. I was most impressed by the style of the authors, Drs. Charles B. Wilkinson and Jeanne Spurlock. They do not apologize for the way they present their views; they describe the facts and data as they see them. The discussion about the impact of racial discrimination on life in general and mental health in particular is well supported with scientific reasoning and devoid of rhetoric. The issues presented in relation to the diagnostic status of black patients in state hospitals are most enlightening. The section dedicated to treatment issues is instructional, particularly the presentation of the late Dr. Walter H. Bradshaw's clinical cases. I also found Dr. Bradshaw's classification of myths regarding blacks quite useful. This chapter makes the book quite worthwhile.

The chapter on Hispanic Americans by Dr. Cervando Martinez leaves much to be desired. Dr. Martinez clearly states that his objective in this chapter was not to do a state-of-the-art review on Hispanic Americans but to stimulate the reader's curiosity on this subject. I think that he should have gone far beyond this. In addition, I think that discussing all three major Hispanic American subgroups (those from Puerto Rico, Mexico, and Cuba) together is a mistake. This chapter should have included more current work being done by experts in the field (1–9).

In discussing Asian Americans Dr. Joe Yamamoto faced a major challenge due to the variety of the Asian American ethnic subgroups. However, he met the challenge beautifully. His description of the discrimination to which he was exposed personally during World War II is very enlightening. He describes the mental health needs of the different Asian American groups, including those from the Pacific islands. He focuses on the variations among them and their different clinical case presentations. This makes his chapter easy to follow and understand. I also found the enumeration of the tests available to diagnose and evaluate Asian Americans to be of great clinical use. The discussion of the intergenerational differences among the Asian ethnic subgroups was also clinically useful.

Finally, the chapter on Native Americans by Drs. R. Dale Walker and Robin LaDue is well conceptualized and well written. The historical perspective offered is very important to the understanding of the content of the chapter. The problems currently confronted in delivery of health and mental health services to Native Americans are well documented and thoroughly discussed. What I liked most in this chapter was the appropriate recommendations made by the authors regarding the potential solution to the health care dilemma of this ethnic subgroup. The appendix provided at the end of the chapter is both instructional and useful.

Overall, I definitely enjoyed reading and reviewing this book. It reminded me of the book written by Dr. Gaw in 1982 (10). What I missed in *Ethnic Psychiatry* was a concluding chapter where the overall message of the book could have been pulled together in conjunction with the individual chapters, particularly since the individual chapters sometimes followed different directions. The editor's main goal was that the book would "serve as a source of practical information useful to mental health providers and planners in understanding, communicating, and responding to the needs of ethnic group patients requiring help." I think that this goal was definitely met. Further, the book points to the need to continuously give high priority to the mental health needs of the different ethnic minority groups who make up the population of the United States. This book should definitely be read and kept handy in one's library.

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The Anatomy of Self: The Individual Versus Society, *by Takeo Doi, M.D.; translated by Mark A. Harbison. Tokyo, Kodansha International (New York, Harper & Row, distributor), 1986, 163 pp., $14.95.*

This is a new contribution by a distinguished Japanese psychiatrist, very well-known to those interested in cross-cultural studies because of his book *The Anatomy of Dependence* (1). In that book, Professor Doi contributed a new insight into the personality of the Japanese. In the close-knit Japanese culture, there is a need to be passively loved (*amae*) related to the very close mother-infant ties that continue through early childhood until the beginning of school. That the Japanese mother aims toward a quiet and contented baby has been well documented by Caudill and Weinstein (2). The mother is constantly present, and perhaps this is the basis for the strong ties between infant and mother in Japan. It certainly explains Doi's emphasis on interdependency in the Japanese culture.

In *The Anatomy of Self,* using his knowledge of Western psychodynamics and the contributions of philosophers and anthropologists, Doi has written a very interesting discussion of Japanese interpersonal behavior. However, the reader is warned that this is a serious discussion of philology, psychodynamics, philosophy, and anthropological issues.

It is difficult to understand how much is lost in the translation from Japanese to English. This is an area of concern because the Japanese title of this book would be translated "Outside [*Omo Te*] and Back [*Ura*]." Perhaps this is not an accurate translation, for *Ura* may mean the lining or what is underneath what is outside, and *Omo Te* may mean what is physical or what is apparent. The analogy of the lining and what is outside is very apt; the two go together. The author makes the point that there is no contradiction between the existence of the outside and the lining, that the two are connected, a part of a whole. This ability in the Japanese language and of the Japanese people to accept opposites has been well documented in their attitudes toward religion (3). The Japanese are able to syncretize various religions, so they do not feel that it is a contradiction to be Shintoist and Buddhist and even, as the occasion arises, to be married in a Christian church.

Because of the difficulties in understanding the translation and the very scholarly scope of this book, it is not to be recommended for someone with only a passing interest in the Japanese culture. For more serious scholars, however, this is indeed a rich contribution that provides something of the flavor of the Japanese. One example is the story about the lady Tekona, a renowned beauty who had many suitors. Two suitors seriously contended for her hand. She felt increasingly in conflict about this situation and finally committed suicide without choosing one or the other. The two suitors then also committed suicide within a few days of each other. Tekona did not commit suicide because she could not decide between the two men but because she had chosen in her heart but could not tell them. She chose death because she was too modest to allow herself to be drawn inexorably into their contest. Tekona is honored and her story moves the Japanese people because of the pureness of her motives. This story has been told for hundreds of years, and to this day there is a Shinto shrine in Chiba that honors the memory of Tekona and her two suitors.

As another example Doi describes a poet-priest whose name was Ryokan (1758–1831). This priest was a Zen recluse who valued his own inner life and showed this in his poetry:

> It is not that
> I would shun completely
> Worldly affairs
> But solitary pleasure
> I find much better.

From my perspective, this valuing of seclusion and privacy may be a response to the fact that the Japanese people live in constant contact with others: from infancy with the mother and subsequently with the rest of the family, in school with the school family, at work with the work family, etc. Most Japanese do not have the luxury of an individual home that is separate, with land surrounding the house for privacy, from neighbors.

To do justice in reviewing this book would take a very long discussion of the many insightful contributions. I hope, instead, that these brief comments whet the appetite of seriously interested colleagues who want to know more about the culture of the Japanese.

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Addictions in the Jewish Community, *edited by Stephen Jay Levy, Ph.D., and Sheila B. Blume, M.D. New York, Commission on Synagogue Relations, Federation of Jewish Philanthropies of New York, 1986, 379 pp., no price listed.*

What is the relationship between religion and drug abuse? Is religion a form of protection and/or treatment for the addictions, and, if so, what aspects of religion serve these functions? Are the putative therapeutic elements of religion to be found in culture, history, social norms, scriptural proscriptions, or prayer or meditation and the exalted states of consciousness that may be entered by these means? What does the use of mind-altering compounds for purposes previously subsumed by religion say about the nature (biological or otherwise) of religious experience? These are several of the questions I hoped might be addressed as I began this book. However, many were left unanswered by this unevenly prepared work.

This volume of collected essays attempts to address the specific problems facing addicted individuals belonging to one religious/ethnic population, the Jews, primarily in the United States. Specific topics covered include etiology, diagnosis, treatment, family issues, and religious implications of addictions in the Jewish community as well as in the larger context of the Jewish religion. Almost all of the authors are from the New York metropolitan area, and many are members of the Task Force on Addictions in the Jewish Community of the Commission on Synagogue Relations of the Federation of Jewish Philanthropies of New York. It is obviously a work of much pride to those who marshalled their energies to focus attention on the addictive problems within the Jewish community. However, the parochialism that the authors feel has made recognition of addictions difficult within the Jewish community has also contributed to substantial weaknesses in this book, which has, as well, some major strengths.

One of the themes running through this work is that of the culturally and religiously proscribed use of consciousness-altering techniques, such as drinking alcohol (especially wine, within the Old Testament tradition). However, in an extreme example, a tradition on one Jewish holiday, Purim, is to become so inebriated as to no longer be able to distinguish Haman from Mordecai (Haman planned a mass extermination of the Jewish population of ancient Persia; Mordecai planned to thwart this attempt). Many Biblical references are made to distinctions between acceptable and pathological drinking and its consequences. In fact, one author simply defines Jewish alcoholism as "getting drunk on non-Jewish occasions," i.e., at times other than those specified by Old Testament text or commentary.

As with any addictive behavior, the cornerstones of resistance to treatment of substance abuse are denial and rationalization. A valuable contribution of this work is the presentation of undeniable evidence that the incidence of chemical dependency in Jews is comparable to that of the general population. Another interesting finding (one that is contradicted in its specifics by several of the contributors) is the refutation of the belief that adherents to the less stringently religious denominations of Judaism are more likely to have problems with addictive behaviors. Fairly comparable rates of adherents to the most traditional branch of Judaism, the Orthodox, and the least traditional branch, the Reform, attend treatment facilities. Even so, opinions vary among the many authors in this book as to the role of "de-assimilation" (my term) from the population at large (i.e., "rediscovering one's Jewish heritage") as an antidote to addictive behaviors.

Whether the Twelve Steps of Alcoholics, Gamblers, or Narcotics Anonymous are applicable to Jewish alcoholics, gamblers, or narcotic abusers is brought up in several chapters. It appears that if Anonymous meetings occur in synagogues and/or with a predominantly Jewish clientele, compliance with and personal relevance of the Steps are enhanced.

The section on drugs of abuse other than alcohol presents considerable evidence that Jews suffer from cocaine-related problems and polydrug abuse as much as does the general population.

This volume suffers from several weaknesses that I feel, at times, could be ascribed to a noncritical, perhaps detrimentally parochial approach. Chapters repeat (and contradict) each other to an unnecessarily great degree. Almost no attempt appears to have been made to "rein in" the authors—chapters range from a 4-page personal reflection to a 52-page epidemiologic research paper with sophisticated statistical analyses of a study with major sampling problems. Several chapters are reprinted articles and chapters or transcripts of lectures. Four brief chapters on compulsive gambling appear out of place at the end of the book and detract from the emphasis on chemical dependency with which this volume is primarily concerned. Written by a Jewish group of authors about addictions in the Jewish community, the book appears to have been written for Jewish readers as well. Many specific Jewish terms, expressions, words, references, and scholars are never introduced or defined, which would leave the reader who has not had a major exposure to Jewish culture missing many major points. The proofreading and editing are of a very low quality. Several pages have so many typographical errors that the ideas they contain are difficult, if not impossible, to understand. There is no index, and references at the end of chapters are presented differently by almost all contributors; some of the reference sections are so casually assembled that the reader would not be able to find the specific references cited.

I have a number of more general questions directed at the raison d'être of this volume; that is, how chemically dependent individuals who are Jewish differ from those who are not Jewish with respect to diagnosis and treatment and how Judaic tradition might be of help in the recovery of these individuals. The issue of contemporary Judaism as a contributing factor to the development of addictive behaviors is entirely avoided. Most of the authors seem implicitly to assume that a return to the fold of Judaism can be a major factor in recovery. On what is this assumption based? It is my belief that man has an inherent drive to relate to and experience what can only be described as "beyond oneself." Some may call this God (in a personal sense), Nirvana (in a "consciousness-based" sense), or love (in an emotional sense). Whatever it is called, I think that Jews have great difficulty finding it in contemporary Judaism. My experience throughout the United States in communities practicing various Eastern religions has been that a very high percentage of the members are Jewish. Most of them had used drugs and/or alcohol in the past to fulfill a yearning that they now refer to as a religious need. This aspect of the etiology of addiction in Jews is nowhere mentioned in this book. Neither is the cabala, the most experiential set of teachings in Judaism, introduced once in this volume. The cabala is a work of a pragmatically mystical nature, a how-to book of religious experience that has been rediscovered by Jews who are looking for a more authentically personal religious experience and who have tried to stay within the Jewish tradition to do so. *Addictions in the Jewish Community* would have been much strengthened and could have offered a good deal more hope if these issues had been raised.

I finished reading this book feeling somewhat frustrated. I did not find much concrete information in its nearly 400 pages that could not have been better summarized in a 20-page review article. I also believe that the emphasis on differences in Jewish addicts obscures the often more relevant clinical similarities between Jewish and non-Jewish individuals suffering from addiction. This book will be useful for practitioners who work with a primarily Jewish clientele and those with an interest in cross-cultural approaches to illness, but I would not recommend it for the general reader of the substance-abuse literature.

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EXPLORING THE MIND

Notebooks of the Mind: Explorations of Thinking (1985), *by Vera John-Steiner. New York, Perennial Library (Harper & Row), 1987, 251 pp., $8.95 (paper).*

This book is an observational, descriptive study of highly creative individuals. It is divided into two sections. Part one, Sources of Thought, covers early developmental experiences ("the beginnings"), the mentorship process ("apprenticeships"), and the development of the cognitive structures necessary to perform creative tasks ("the invisible tools"). The second part, The Languages of the Mind, has chapters on visual thinking, verbal thinking, the languages of emotion, and scientific thinking. The book is reasonably well written and easy to follow.

Any study of creativity is difficult. First, due to the rarity of creative individuals, cohort studies are not practicable. Even when the case-control method is applied, the very nature of creativity creates diversity within the creative group that can confound earnest attempts to understand. This book appears to make several contributions. It attends to the different types of thinking that could go into the creative process. It expands its inquiry to include creative women as well as men. Finally, it devotes some attention to the passion involved in the creative process.

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Exploring the Concept of Mind, *edited by Richard M. Caplan. Iowa City, Iowa, University of Iowa Press, 1986, 150 pp., $15.95.*

The literature on mind-body problems seems to increase exponentially. A certain tendency to integrate different opinions on the relation between the brain and behavior characterizes a great many of these publications. This book, too, can be considered a multidisciplinary attempt at integration. It is a report on a symposium on mind-body problems organized by the University of Iowa. The symposium emphasized the relationship between science and the humanities.

The collection of essays is introduced by the editor, who is Professor of Dermatology, Associate Dean for Continuing Education, and founding director of the Program in Medical Humanities at the University of Iowa College of Medicine. His interest in mind-body problems is evident in his extensive and capable introduction. He sees not only a dualism in the opinions about mind and body but also a separation in the interdisciplinary communication that probably can be traced back to Cartesian dualism. The discourses of science and the humanities seem to be separated by a nearly unbridgeable gap. The assertion that this gap does not exist in medical science is naive. An example of misunderstanding on this level is Sulloway's book about Freud (1). On the basis of an analysis of the Freudian discourse, Sulloway claimed that Freud essentially was a materialist. Sulloway, guided by a strict interpretation of Freud's words, did not understand the essence of Freud's metaphors. This misunderstanding reveals an important problem in Western thinking, especially in the medical sciences, that will take many decades to resolve. We are now involved in a dialogue between the most important tendencies in Western thinking: materialism and mentalism. Therefore, we must consider *Exploring the Concept of Mind* in this perspective—as an attempt to bridge the dualistic gap.

After the excellent introduction by Caplan, the following subjects are raised: how old the mind is, how old consciousness is, modeling of mind-brain relationships, the language of pain, where creativity is, the literary imagination, and whether minds are developed or created. These subjects are very interesting, but they are not connected to one another. Only the editor attempts to associate science with the humanities. This effort is worth reading.

All of the authors of the essays are in the humanities except one: Antonio Damassio is an internationally well-known neurologist. Damassio gives an exposition on the newest ideas about the working brain. On that level his essay is readable and up-to-date, but I could not comprehend his comments on the relationship between mind and brain.

After the introduction, I enjoyed Doris Grumbach's essay, "The Literary Imagination," the most. She is obviously used to building up an argument and loads her essay with examples from literature and a pleasant dose of humor. She compares the mind to a compost heap made up of everything one hears, sees, thinks, dreams, reads, and remembers. At first this metaphor was repugnant to me, but later on I could appreciate it.

On the whole, this is a pleasant book in which different American authors show their philosophical interest and the extent of their reading on mind-body problems.

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The Anatomy of Illusion: Religious Cults and Destructive Persuasion, *by Thomas W. Keiser and Jacqueline . Keiser. Springfield, Ill., Charles C Thomas, 1987, 144 pp., $25.25.*

This book is a well-written, easy-to-read overview of the phenomenon of totalitarian religious cults in America. Although not a particularly comprehensive or scholarly treatise, it is honest and based on clinical experience. The Keisers, a psychologist and a social worker, describe their own work with former cult members and families of members. They have been influenced by what they have seen of the harm that cults can do. They have not been intimidated by public relations smoke screens used to disguise the exploitative nature of cults. Nor have they been swayed by pronouncements made by social scientists who have been taken in (literally or figuratively) that cults are safe and sanitary. Having reviewed some—though not all—of the literature, the Keisers undertake to describe cults, tell how they control members, and discuss the social impact of these controlling techniques. The Keisers then offer a series of conclusions and theories that, although interesting, are not substantially different from those of others in the field of religious cult research.

The Keisers begin with a brief overview of the current controversy surrounding the cult phenomenon. Opinions span the extremes: cults are completely benevolent or utterly malevolent; they are destructive or therapeutic. At the center of the controversy is the issue of religious freedom and the notions of brainwashing, mind control, coercive persuasion, and thought reform. Some critics of cults believe that most if not all of these groups use unethical means to recruit and hold their members. The Keisers' position, although less extreme, is not uncritical.

Following a brief review of the scientific literature on brainwashing, the authors suggest that cults gain control over their members, not by brainwashing but, rather, through a process they choose to call "destructive persuasion." Individual case reports are used to illustrate how recruitment or conversion is accomplished by this technique. It involves two strategies: manipulation of needs and control of information. (Only in rare cases do most cults use physical restraint.) The authors postulate that manipulation of needs and control of information are designed primarily to change members' basic beliefs and attitudes rather than to effect radical personality changes.

The way in which the authors orient their ideas to those of other workers in this field appears to be not so much selective as haphazard. For example, they were obviously influenced by the book *Snapping,* by Flo Conway and Jim Siegelman (1), and are quite frank in identifying their connection to these beginnings. They try to provide a learned discussion of brainwashing in terms of William Sargant's attempts to apply Pavlovian biology to the process of conversion, mind control, or brainwashing. They also review the ideas of Joost Meerloo. However, having quite properly rejected the propositions of Sargant and Meerloo, they go on to provide a "new perspective" that is not really very original and gives little reference to the insights of contemporaries who are prominent in the field. Robert Lifton and Edgar Schein are mentioned only in passing. The most important contemporary contributors to the literature on cults are not cited at all. How can a psychologist involved in rehabilitating cult victims totally ignore the contributions of Margaret Singer? Another psychologist, Michael Langone, editor of *Cultic Studies Journal,* has written widely in this field. *Cultic Studies Journal,* now in its fourth year of publication, has thoroughly gone over the ground that the Keisers apparently think is new. A new book that ignores most of the literature of the last 10 years does not reflect good scholarship. I make this point so that psychiatrists will not treat this book as a scholarly treatise. It is, rather, a sincere and objective account of the clinical experience of well-qualified mental health professionals in a field still not well understood by either the professions or the public.

In the final section, the Keisers discuss legal aspects of the cult controversy. The veneer of religion provides cults with protection under the First Amendment of the Constitution. Behind this veneer is the hidden agenda of cult leaders: the acquisition of money and influence. Unfortunately, the law cannot distinguish between sincere promotion of religious beliefs and strategic ideologies used to amass wealth and power. There are very few legal remedies for cult victims and even fewer legal means for deeply concerned family members to extract their relatives from cults. Examples are provided in which the use of conservatorships, writs of habeas corpus, and involuntary hospitalizations have been tried, but so far only with limited success. The legal risks of "deprogramming" are discussed, and the appendix includes a young former cult member's account of her own successful rescue. However, several tragic case histories illustrate that the damage done by cults can be irreversible. The Keisers conclude that their greatest objection to the use by religious cults of "destructive persuasion" is that it impairs individual adaptability, damaging the good judgment of their members. By systematically cultivating illusion, discouraging curiosity, and censoring alternative sources of information, cult leaders substitute their own authority for the personal responsibility and self-determination of their followers.

In summary, this book is a useful addition to a small but growing body of literature trying to clarify some of the depredations committed by cultic organizations in the name of religion. Its value lies mainly in the recitation of clinical experience rather than in any new theoretical contribution. It should be welcomed by those in psychiatry who are seeing more and more of the victims of totalitarian cults and who should realize that cultism is an important and growing problem.

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LAW AND ETHICS

Defendant: A Psychiatrist on Trial for Medical Malpractice—an Episode in America's Hidden Health Care Crisis, *by Sara C. Charles, M.D., and Eugene Kennedy. New York, Free Press, 1985, 224 pp., $17.95.*

At a time of concern about escalating claims of medical malpractice, these authors have written an interesting account of one psychiatrist's experience as a defendant in a malpractice suit. A young woman in Dr. Charles's care for the treatment of borderline disorder jumped off a roof in an unsuccessful suicide attempt, leaving her paralyzed and confined to a wheelchair for life. Dr. Charles continued to treat the patient after the accident, but the patient later brought a lawsuit alleging negligence. The patient claimed that Dr. Charles had admitted to her father that she may have made a "clinical error" (p. 46). Dr. Charles countered that there was no such error. The suicide attempt could not have been predicted. Furthermore, her understanding of what had transpired between her and the patient in therapy was quite different from what the patient alleged had happened.

After informing the reader of the facts and basic allegations and presenting a brief overview of negligence law, the authors reconstruct the subsequent trial, including verbatim testimony by the plaintiff, her family, interested others, the defendant, and expert witnesses. All this is presented in a consecutively unfolding drama with selective summaries of information from depositions as well as descriptions of the behavior of the legal protagonists, the attorneys. The result is a fascinating firsthand account of the conduct of a trial of psychiatric malpractice, a trial that eventually resulted in a victory for the defendant. But the trial and its preparation are demonstrated to have been time-consuming, exhausting, and disturbing for the defendant. This volume joins another recent popular account of a malpractice suit and its impact on the physician (1).

As might be anticipated, two versions of what occurred, who said what, why they said it, and the diagnostic and therapeutic process emerge. Was the patient suffering from a biological depression requiring medication or did she have borderline personality disorder? Did she jump because she was biologically depressed or because she feared that her father was coming to Chicago to hospitalize her against her wishes? Could she have controlled her behavior if she wanted to? One of the strong points of this book is that it gives sufficient primary material and perspectives from both sides so that the reader is drawn into the drama. To some extent the reader has the opportunity to become a juror in deciding what really happened. Although the writing is at times melodramatic, even novelesque, the authors believe that this information accurately reflects what went on at the trial, capturing the emotional tone of the participants. The reader is exposed to the hyperbole and antics of the plaintiff's attorney, in contrast to the cool, rational mien of the defendant's attorney. Inevitably, the recitation of the trial (and selectivity of the information) leaves some things hanging, factual questions that are never answered because of the legal process, the rules of evidence, and the strategies of the participants. As the authors apparently intended, the dialogue illustrates that although trials settle disputes and thereby achieve some rough sense of justice, the truth may not always emerge in such a process.

I believe that this volume is an important contribution to the literature of malpractice. Even though it has flaws (at times the tone is self-serving and the reader wishes for more exploration of the feelings of the defendant), the major purposes of the volume are achieved. The firsthand accounts of the trial and the sections dealing with primary data are more successful than the latter portions of the book. In the concluding section, the authors present their view of the facts and background of the present malpractice litigation crisis, summarizing theories regarding why this crisis has occurred. This latter portion of the volume, relying on secondary data interwoven with the authors' theories, does not break new ground.

A simple virtue of this book is that it has been written. It is testimony to the authors' continuing involvement and fascination with the subject of malpractice, which has resulted in other publications, including an empirical study and survey (2). This book is a "working through" for Dr. Charles and her husband (Mr. Kennedy) of the painful process of having had a patient turn against her, having her skills questioned in a public adversarial forum, and the possibility of having her work distorted, presenting a risk to her psyche and her career. The authors demonstrate the impact of an allegation of malpractice against a physician who views herself as clinically responsible and who has delivered good care in a difficult case. Psychiatrists who have been sued or who fear that they may be at some future time will find some comfort here.

As former U.S. Attorney General Benjamin Civiletti (3) noted concerning the lawsuit explosion, few jurisdictions provide a reasonable framework for resolving disputes. The current system offers the worst of two worlds: "We have a fault system, with a bent toward no-fault compensation" (3). Perhaps this is what most troubles the authors. Even though the defendant views herself as without fault, the process and the outcome may suggest otherwise. Legal and insurance company practices have conjoined to encourage actions irrelevant to whether one is a good doctor. This book is an attempt by Charles and Kennedy to demonstrate that claim in a particular case.

I recommend this book to psychiatrists and others who are concerned about physician-patient relationships and their potential distortion in litigation. Unfortunately, more of our colleagues will probably be having similar experiences in the future.

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Legal Issues in Pediatrics and Adolescent Medicine, 2nd ed., *by Angela Roddey Holder. New Haven, Yale University Press, 1986, 357 pp., $35.00.*

Many books are approached with great expectations, but few deliver on their initial promise. Holder's book is the delightful exception to this rule. It is a comprehensive and thorough review of the history of law regarding minors and its interface with pediatric and adolescent medicine. It is a surprisingly readable book with a natural flow to the writing that helps simplify the many complexities inherent in this complicated and sometimes extremely convoluted subject. Three almost alien systems—law, medicine, and developmental changes—converge on the individual child or adolescent in particular situations.

Law approaches these situations and problems with the rational, dispassionate logic of King Solomon. It comes with geopolitical and historical baggage that makes it slow to respond to new trends and scientific discoveries.

Medicine, both pediatric and psychiatric, views these problems within the medical model. It uses physiology, biochemistry, and medical science to cover the inherent underlying paternalism of the doctor-patient relationship. This is applicable even in the areas where there is more than one identified patient, such as the pregnant adolescent or divorcing parents with more than one child. Physicians are inherently paternalistic by training and carry this personal and professional presentation with them even when confronting lawyers and judges. The brilliance of this book is that it deals directly, albeit subtly, with this phenomenon without affronting the well-intentioned physician who may be reading it.

Finally, by its very nature, development is not static; it presents a constant challenge to the physician, lawyer, or lay person who tries to understand a given child in a given situation. Not only is human development not static, but individual development may vary greatly from one person to the next. Further complicating the picture, an individual may develop at varying rates within different organ systems and from one developmental stage to the next throughout life. The family unit from which the child comes may also have developmental aspects that play important roles in the ultimate decision of any given legal situation. As part of development, considerations for remediation of retarded development of pathological conditions must also be addressed.

The straightforward aspect of this book's chapters is most apparent in the complicated convergence of these very different systems. The book is extremely well organized, beginning with conception and prenatal issues, a most timely topic of great modern significance. It ventures carefully and solidly into genetics and new procedures, discussing each fully with the time-honored aspects of physicianhood and responsibility. It is here and in the area of research issues that this book is at its peak. These are the areas where the law has been most cautiously advancing and social and religious ethics most debated.

My only criticism of this fine book is the relative lack of focus on child and adolescent psychiatry, particularly child and adolescent forensic psychiatry. Both the American Academy of Child and Adolescent Psychiatry and the American Academy of Psychiatry and the Law have dealt extensively with many of these areas of legal quandary: custody, various competencies, and delinquency. Specially trained psychiatrists are better equipped to evaluate these situations than most pediatricians. Schowalter, Weithorn, and others were included in this book, but perhaps this was insufficient. Elissa Benedek or Diane Schetky should be referenced in any book about medicine and the rights of children.

However, this criticism does not imply that this fine and amazingly comprehensive book has egregious errors and flaws. This is clearly an outstanding and extremely important work that should receive the widest possible readership just as it is written. The issues are clearly relevant to pediatrics, child psychiatry, and related disciplines as well as the legal profession. In addition, this book is appropriate for any learned person who wants to understand these complicated problems arising in modern society and medicine. It should be read not once but at least twice and should be referenced often.

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Mental Disorder and Legal Control, *by Philip Bean. New York, Cambridge University Press, 1986, 207 pp., $49.50.*

This book examines the changes introduced by the 1983 British Mental Health Act in the control of the mentally disordered from the perspective of a social scientist.

As in the United States, the law on civil commitment in Britain goes in cycles. In England and Wales the 1890 Lunacy Act established legalism; that is, admissions to mental hospitals and treatment in those hospitals were to be governed by legislation and controlled and supervised by government bodies. When legalism was found to be unworkable, mainly because of the stigma said to be associated with mental hospital admissions and the manner in which legalism prevented patients from entering mental hospitals except by the courts, the 1930 Mental Treatment Act was introduced. That act allowed some patients to enter the hospital voluntarily, that is, without certification. Some 30 years later, in 1959, legalism was swept away entirely, to be replaced by a medical view of mental disorder. The 1959 Mental Health Act saw mental disorder as the province of the medical profession. The 1983 act, however, goes back to legalism, this time focusing on the legal rights of patients.

The 1983 act was influenced by the recommendations of a number of government committees, notably the Committee on Mentally Abnormal Offenders and the European Commission on Human Rights of 1980, together with various research reports and the activities of certain pressure groups, notably the National Association for Mental Health.

In this small but expensive book, Philip Bean, senior lecturer in the Department of Social Administration and Social Work at the University of Nottingham, covers the major aspects of the legislation—the compulsory admission procedure for nonoffender patients, police powers, guardianship, consent to treatment, offender patients, and general rights of the patient. These topics are covered in nine chapters, each of which can be read independently with the exception of the opening chapter, which sets the boundaries and defines the terms.

If past experience is anything to go by, the law will be honored more in the breach than in the observance. Enforcement of the law, in large measure, would bring the operation of a mental hospital to a standstill.

The 1983 act has produced an increasingly muddled and confusing situation. Two illustrations will suffice. First, the act calls on a social worker to act as a diagnostician in making an application for admission: the social worker is to state "the type of mental disorder" in the application. Second, the act includes "psychopathic disorder" that results in "abnormally aggressive or seriously irresponsible conduct on the part of the person concerned" within the definition of mental disorder justifying commitment.

The book is well written and makes many interesting observations about mental health legislation. At this stage, more questions are asked than answers provided. For the American observer, however, it's déjà vu.

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Ethical Issues in Psychosurgery, *by John Kleinig. Winchester, Mass., Allen & Unwin, 1985, 147 pp., $24.95; $9.95 (paper).*

During this century the field of ethics has changed from the study of moral philosophy and its questions of what is right and what is good to an examination of the meaning and form of the questions asked. In this book John Kleinig applies the methodology of contemporary philosophy to diagnosis and treatment in psychosurgery. He sees his task as clarifying particular issues rather than taking a position on whether psychosurgery should be performed. Nevertheless, implicit in the way he frames his analysis is the suggestion that he is skeptical about the claims of its efficacy. He stresses being cautious in deciding when and on whom to perform the various procedures.

He starts out by comparing psychosurgery and neurosurgery, noting that neurosurgeons remove tissue with cellular pathology while psychosurgeons assume pathology to be at the subcellular level of receptor sites and neurotransmitters. Therefore, contrary to their critics' charges, psychosurgeons, like neurosurgeons, do not operate on healthy brain tissue, although knowledge of subcellular function followed the first psychosurgical operation by many years.

The author then reviews the history of the procedures, beginning with the frontal lobotomy first performed by Egas Moniz in 1935. He questions the accuracy and validity of psychiatric diagnosis and supports the *DSM-III* move toward standardization, since psychiatric descriptors are "normatively problematic or too vague to offer protection against psychiatric overkill" (p. 21). He wonders how one procedure, such as frontal lobotomy, could have been used for more than one diagnosis. He adds that because psychiatric disorders appear all too often in the form of some type of social dislocation, the practice of psychosurgery should be carefully monitored.

The author observes that critics are particularly sensitive to the irreversibility of the procedure and its implications for a patient's personal growth and development. We still attach a Cartesian importance to operating on the brain; it remains too close to the soul. Unlike an amputation or colectomy, cingulotomy and the other procedures seem somehow to have the potential to change a person's identity or sense of self. They appear to violate the sanctity and inviolability of the mind-brain.

Since these procedures can threaten our sense of autonomy, it is not surprising that they are used as a last resort. The author points out that what might be the last resort for one physician may not be for another, depending on their areas of specialization, their capacity to devise new treatment plans, and their ability to tolerate clinical uncertainty and frustration.

Patients may also be more desperate than their caregivers and seek to have the operation performed before it is recommended. Although Kleinig carefully examines the issue of informed consent, he neglects the problem of the patient who searches endlessly to find someone to perform the operation. Again because of the special meaning attached to operating on the mind-brain, the right to treatment and the right to refuse to give treatment take on additional importance in this area. For the author the problematic nature of psychosurgery argues against the right to treatment for noncompetent patients even if guardians consent. He believes a person "can't consent to mayhem or other self-destructive conduct." A person's wish to sacrifice key elements of his or her personality is insufficient reason to assist him or her (p. 60). The author refers to the uncertain theoretical bases for the various procedures when he questions the validity of consent. Concepts such as the restoration of homeostasis between limbic system and neocortex are too vague. The early rationale for frontal lobotomy was that the operation would dampen affective expression. Because emotions involve complex interactions of perception, memory, and action, the author does not see how a particular emotion can be curbed by surgical means, even within the limbic system. He is concerned that surgical intervention for the aggression associated with temporal lobe epilepsy may be a form of social control, since the aggression involves behavior that by definition is deviant.

Kleinig finds it difficult to determine the effectiveness of the treatment. Symptom improvement and manageability are not good criteria because they can involve costly trade-offs in terms of increased passivity and lowered expectations for career goals. The data in published studies are deficient because of the heterogeneity of diagnoses and procedures.

The author concludes that although psychosurgery may and probably does have a legitimate place, there has nevertheless been ample cause for concern about some of its uses. He recommends a sensitive interplay between doctor, patient, and society; the establishment of review panels; and restriction of the procedures to specialized units. Having carefully reviewed the history and occasions for surgery, the different types of operations, and the various anatomical sites for the procedures, he offers this balanced conclusion, which is difficult to question.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

The Seeking and Liking Potentials of Alprazolam

SIR: The most reliable data on the potential for abuse of benzodiazepines are yielded by studies of subjects who have a history of benzodiazepine abuse (1). Such studies are typically designed for between-drug comparisons (2) or estimations of dose preference (3).

We examined the potential for abuse of alprazolam and diazepam in five inpatients (four female, one male; mean ± SD age=38.6 ± 7.2 years) with long-term benzodiazepine dependency (mean ± SD duration=9.6 ± 2.2 years). Four patients were dependent on bromazepam (mean ± SD daily dose=27.8 ± 11.2 mg; mean ± SD diazepam equivalent= 60.0 ± 24.2 mg), and one patient was dependent on oxazepam (120 mg/day; diazepam equivalent=25 mg). None of the patients had had experience with either diazepam or alprazolam. Their medications were discontinued on the day before the study began. All five patients gave written informed consent for the study.

Over 4 days the following drug design was applied: diazepam, 5 mg t.i.d., was given on day 1 and day 4; on day 2 the morning medication and on day 3 the noon medication of 5 mg of diazepam was replaced by 0.5 mg of alprazolam, which is an equally potent hypnosedative and anxiolytic. The drugs were dissolved in orange juice, and the patients were blind to the drug application. One hour before the last administration of drugs for the day, the patients completed a test battery including a visual analogue scale for estimating drug seeking behavior (17-point scale: 0=would never take it again, 16=would very much like to take it again), a 5-point liking scale (1=did not like it, 5=liked it very much), a choice test (preference for morning or noon medication), and a withdrawal symptom questionnaire (4). Blood samples were drawn on days 1 and 4 to determine serum benzodiazepine levels (by gas-liquid chromatography).

During the entire study period, scores on the withdrawal symptom questionnaire remained unchanged and indicated a very mild withdrawal reaction in all five patients. Toward the end of the study, serum bromazepam and oxazepam levels were undetectable, diazepam levels remained constant, and desmethyldiazepam levels were slightly increased. Both the liking and seeking potentials of alprazolam (mean ± SD=56.7% ± 3.3% and 84.3% ± 8.2% of the maximum scores, respectively) were significantly higher than the respective potentials of an equivalent dose of diazepam (37.8% ± 6.2% and 61.8% ± 10.6%, respectively; $t=5.25$, $df=7$, $p<0.005$, and $t=3.31$, $df=7$, $p<0.02$, respectively, two-tailed tests). Most sensitive, however, was the discrimination between alprazolam and diazepam in the drug choice test: patients indicated a preference for alprazolam in 90% of their choices.

These data suggest that in patients with a long-term, high-dose dependency on bromazepam or oxazepam, alprazolam has a higher liking and seeking potential than an equally potent dose of diazepam. These results were derived from patients with constant serum diazepam levels and mild benzodiazepine withdrawal reactions due to the reduction in their previously high doses of benzodiazepine during the study period.

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Administration of ECT 4 Years After Aortic Aneurysm Dissection

SIR: To our knowledge, this is the first report of the administration of ECT to a patient with a history of a dissecting aortic aneurysm. Because ECT causes increased blood pressure (1), aortic aneurysm is a relative contraindication for use of ECT. We know of three prior reports of ECT administration to patients with aortic aneurysm (2–4), but none of these patients had a history consistent with dissection.

Mr. A was first hospitalized at age 76, 7 days after an episode of sharp back pain which lasted 30 minutes and woke him from sleep, pale and sweating. An aortogram showed a probable small thrombosed dissecting aneurysm originating in the superior aortic arch and extending down the distal aorta to the level of the diaphragm. Mr. A was treated medically and was discharged on a regimen of propranolol, methyldopa, and chlorthalidone for control of his blood pressure.

Four years later Mr. A was readmitted. He knew his wife had died yet he continued to talk to her and feel persecuted by her. He had lost 20 lb., was anhedonic, slept poorly, had diminished self-esteem, and wished to die. He had been taking metoprolol and spironolactone with hydrochlorothiazide.

His blood pressure was 140/100 mm Hg supine and 125/100 mm Hg erect. An ECG revealed a bifascicular block and an old inferior wall infarction. A CAT scan of the head revealed right parieto-occipital and frontal infarcts and generalized atrophy. Vitamin B_{12}, folate, and thyroid function test results were normal.

The spironolactone with hydrochlorothiazide and the metoprolol were slowly stopped. Mr. A was unable to tolerate amitriptyline, haloperidol, or diazepam. He continued to be depressed, crying and losing weight.

After informed consent was obtained from the patient and his family, ECT was begun, with a cardiologist in attendance. Blood pressure was monitored with an automated cuff. Atropine, 0.5 mg i.m., methohexital sodium, 60 mg i.v., and succinylcholine, 40 mg i.v., were given (Mr. A's weight was 155 lb.). ECT was administered bilaterally with a MECTA stimulator. Two days after the second treatment, Mr. A reported he had had transient, nonradiating substernal chest pain. There were no changes in his cardiac enzyme levels, his ECG, or the appearance of his aorta on the chest X-ray. His blood pressure was lowered slightly by administration of hydrochlorothiazide, 25 mg p.o. every other day, and 2 in. of nitroglycerin ointment applied topically before subsequent treatments. This reduced his maximal posttreatment systolic blood pressure from 210 to 190 mm Hg.

After the sixth treatment, with no improvement, treatments were stopped. Mr. A continued to decline and was placed in a nursing home; he died 3 months after the last treatment.

Husum et al. (5) reported giving ECT to a patient with an intracranial aneurysm. They eliminated vascular reactivity by prior administration of hydralazine and propranolol. We did not do this because Mr. A had tolerated a systolic blood pressure of 190 mm Hg during episodes of intense crying. In addition, the dissection had occurred 4 years previously.

This report supports the safety of ECT for patients with severe cardiovascular disease, including a history of dissecting aortic aneurysm, when other treatments have failed and depression is profound and unrelenting.

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Mania Associated With Procainamide

SIR: Mania in the elderly is usually associated with organic precipitants, which commonly include drugs, metabolic disturbances, infection, and neoplasm (1). We wish to report the onset of mania associated with administration of procainamide.

Ms. A, a 73-year-old white woman with hypothyroidism and well-controlled hypertension, was taking levothyroxine sodium, atenolol, and chlorthalidone. Although she had no personal history of psychiatric illness, she had a brother with bipolar disorder and her family described her as an excessive talker.

Six weeks before her admission to the hospital, it was shown by Holter monitor that Ms. A had unifocal premature ventricular contractions (<10 per minute); she was prescribed procainamide, 500 mg q.i.d. Four weeks before her admission, Ms. A noticed diffuse myalgias and lethargy. Two weeks before her admission, her cardiologist noted that she had pressured speech and psychomotor agitation. At that time she had an antinuclear antibody titer of 1:256 with a diffuse banding pattern. Due to an increase in her logorrhea and lack of sleep for 5 days, Ms. A voluntarily presented herself for psychiatric hospitalization.

On admission she was alert and oriented and was wearing layers of colorful clothes. She had pressured and tangential speech, inflated self-esteem, flight of ideas, euphoric mood, and psychomotor agitation. She demonstrated no signs of dementia.

Ms. A was afebrile and had normal vital signs. A physical examination revealed multiple tongue ulcers, bilateral confluent purpura over her lower legs and ankles, and edema in the left ankle.

Admission laboratory results were positive for the VDRL test. Results of a fluorescent treponemal antibody test were negative. Results of other laboratory tests—which included routine plasma chemistries, thyroid function tests, lupus erythematosus cell preparation, and determination of anti-native-DNA antibodies, rheumatoid factor, and complement levels—were within normal limits. Her plasma procainamide level was 3.6 μg/ml, her *N*-acetylprocainamide level was 2.8 μg/ml, and the combined level was 6.4 μg/ml (normal=5–30 μg/ml). A chest X-ray and CAT scan of the head were within normal limits. An ECG showed that the patient had a normal sinus rhythm.

Given Ms. A's appearance of having acute mania and a possible drug reaction, on the second day of her hospitalization the procainamide was discontinued, and she was treated with 3 mg of lorazepam over 48 hours. She continued to take all her other medications. Twenty-four hours after the procainamide was discontinued, Ms. A's heart rhythm converted to stable bigeminy. After 48 hours without procainamide, she was notably less manic and the lorazepam was discontinued. Ms. A continued to show a decrease in manic symptoms and was discharged on day 6 of hospitalization with an improved sleep pattern, normal flow of speech, and a decrease in leg purpura and edema. Follow-up 2 and 4 weeks after discharge showed no relapse into manic behavior.

This patient, who had had no previous psychiatric history, developed acute mania associated with the use of procainamide at nontoxic levels. Procainamide has previously been reported to induce psychoses characterized by paranoia, agitation, and hallucinations (2). To the best of our knowledge, this is the first report of mania associated with procainamide.

The appearance of an adverse drug reaction is also significant. The decrease in leg inflammation after discontinuation of procainamide suggests a hypersensitivity to the medication. Myalgias, angioedema, and skin rashes have been associated with procainamide (3). Although Ms. A developed positive antinuclear antibody titers, this effect is seen in 50%–80% of patients taking procainamide (4). The full clinical picture of drug-induced lupus was not evident.

This case demonstrates the appearance of mania and an apparent idiosyncratic drug reaction upon use of procainamide. Clinicians should be aware of mania as a possible side effect of procainamide.

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Potential Spread of AIDS to Fundamentalist Spouses

SIR: I wish to acquaint readers with a generally unacknowledged potential vector for the transmission of acquired immune deficiency syndrome (AIDS) from the homosexual to the heterosexual population.

The wife of a couple presented to me in private supervision was a member of a fundamentalist religious sect. Her husband had renounced homosexual activity at age 22, in the setting of his conversion. He had participated vigorously in various homosexual activities since late adolescence.

Several months after the marriage, the husband returned to episodic homosexual encounters in bars, bathhouses, and gay movies, which continued over the next year. He kept knowledge of these from his wife, but she grew increasingly suspicious after many unsubtle hints. When she finally confronted him, he admitted his extramarital adventures immediately. The couple were referred for counseling by their private physician.

The wife had been unknowledgeable about sexual matters, came to the marriage a virgin, and was poignantly naive about the possibility of contracting AIDS from her husband. Serological testing of both partners produced negative results. The husband resolved to halt his homosexual activity and to resume regular sexual relations with his wife (intercourse had been infrequent during the period of his surreptitious homosexual activity). It was clear he viewed marital sex as an obligation rather than a pleasure. Because of their religious beliefs, the couple had not been using any method of birth control. Despite their having been advised that the husband might still be or might yet become a carrier of AIDS, it seemed likely that intercourse would take place as before, without the protection of a condom. The couple abruptly terminated counseling after two visits and sought help from a lay counselor of their own faith.

Many complex, ominous issues are raised by this case. I shall cite but a few:

1. The possibility that such situations are becoming more common with the recent upsurge of fundamentalist activity. (Under the rubric "fundamentalist" I include not only "born-again" Christians but also followers of mainstream or idiosyncratic faiths who interpret their particular scripture as received truth, have conversion experiences, and so on. Abhorrence and proscription of homosexual behavior seem particularly stringent among fundamentalists.)
2. The probability that clinicians will not see many fundamentalists presenting this problem. These individuals do not easily reveal their sexual practices to strangers. If they seek counseling at all, it is more likely to be with lay coreligionists or ministers.
3. The relative or absolute inability of a fundamentalist couple to seek divorce when it finally appears that the husband cannot renounce his sexual predisposition (1, and personal communications from Richard M. Childs, M.D., and E. Mansell Pattison, M.D.).
4. The possibility that the husband may choose not to inform his wife of lapses, while continuing cohabitation.
5. The possibility of transmitting AIDS to the fetus of a woman committed to carrying pregnancy to term at all costs.

It behooves therapists of all persuasions to maintain a high level of vigilance whenever a fundamentalist couple give an intimation that the husband may be struggling with homosexuality. It goes without saying that the utmost respect must be deployed in dealing with such delicate circumstances. A willingness to work further with a lay or professional counselor of the couple's faith will probably be useful.

Discussing the dangers of AIDS cannot be avoided but should be undertaken with exceptional tact. Serological testing should be recommended for both partners when clear evidence exists that the male spouse is at risk.

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More on the Psychodynamic Formulation

SIR: In our article "The Psychodynamic Formulation: Its Purpose, Structure, and Clinical Application" (1), we cited the recent book by MacKinnon and Yudofsky, *The Psychiatric Evaluation in Clinical Practice* (2), in which these authors stated that the case formulation is principally for the education of the clinician, for clinical case conferences, and for a confusing or difficult case. The authors have pointed out to us that this citation may have been misleading. Although we indicated that Drs. MacKinnon and Yudofsky agree with the importance of understanding a patient's psychodynamics and we also indicated that they were referring to a more detailed and complete case formulation than the much briefer psychodynamic formulation we described, in the context of our article the reader might erroneously conclude that Drs. MacKinnon and Yudofsky do not believe that the psychodynamic formulation should be written or that they believe it to be useful only for psychoanalytically oriented psychotherapies. These are common misconceptions but are certainly not the views of these authors. In fact, their full discussion made abundantly clear their belief that written formulations are important in a wide variety of clinical situations. They argued this cogently and persuasively in their text and provided detailed and rich examples.

One of us (R.M.) stated in the foreword to their book that it "is certainly one of the finest introductions to the basic knowledge the psychiatrist will want at his side as he approaches his patients. The field is indebted to [them] not only for the comprehensive scope of their work, but for the elegance of its presentation as well." We are pleased to direct the interested reader to their excellent book for further discussion.

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SIR: My compliments to Drs. Perry, Cooper, and Michels for their long-needed article on the psychodynamic formulation. It provides a sound, cost-effective rationale for using the "medical model" for effective diagnosis, prognosis, and selection of treatment. In addition to greatly benefiting our patients, this would enhance teaching programs.

In our paper "Structure and Process in Limited-Goal Outpatient Psychotherapy" (1), my colleague and I proposed a similar conceptualization. As in the study by Dr. Perry and associates, our psychiatrists made formulations based on the particular school of psychoanalysis they had attended. We found that no matter what the individual theoretical persuasion might have been, the actual verbal interpretive communications with patients were remarkably similar within the group. All agreed about the importance of their psychodynamic formulations in achieving treatment goals.

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ABRAHAM S. LENZNER, M.D.
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SIR: It is with interest and some pleasure that I note the article on the psychodynamic formulation by Drs. Perry, Cooper, and Michels. As someone who has taught psychiatric interviewing to medical students and psychiatric residents for several years, I wholeheartedly concur with the authors' argument that the written psychodynamic formulation is an important and underused educational and clinical tool.

It seems to me, though, that there is a more basic problem which needs to be addressed before the written psychodynamic formulation can be successfully executed and used. In my experience, as the "medical-phenomenological model" of psychiatric diagnosis and treatment has become more fashionable, the psychodynamic interview has become more and more unfamiliar to psychiatric trainees. Residents are now being taught that one can elicit all of the information necessary to make an adequate diagnosis and assessment of a patient by administering a structured, prepackaged interview or by having the patient complete a questionnaire. We have taught residents to overvalue content at the expense of an appreciation for the process of an interview and the invaluable information that can be gleaned from careful observation of the nuances of a patient's speech and behavior and our own response to the patient. Residents are being taught to listen for hallucinations and delusions rather than to listen to the content of the patient's hallucinations and delusions as indirect expressions of the patient's wishes and fears. As the authors suggested, thoughts that may result from a disordered neurotransmitter system are nevertheless the person's thoughts and must be taken as meaningful to that person.

It is imperative that, along with stressing the psychodynamic formulation as a learning and clinical tool, we recommit ourselves to teaching trainees to listen with the "third ear." We should begin to reemphasize some of the basic classical works on interviewing that have unfortunately fallen somewhat by the wayside in recent years (1-3). We must reaffirm our professional commitment to treating patients as whole human beings with complex needs, wishes, fears, and personalities that must be understood before we can provide optimal care.

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VICTOR SCHWART, M.D.
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SIR: "The Psychodynamic Formulation" is a beautiful example of the dilemma of our Association in trying to make peace between psychoanalysis and psychiatry, a medical discipline. The dynamic formulations are presented without supporting evidence. On page 545 we are told that the departure of her youngest child played a role in the onset of the mother's depressive episode. All prospective studies that have tried to find precipitating psychological causes for cyclical major depressive disorder have failed. In the next case, we are told about the meaning of a schizophrenic patient's delusions; again, no supporting evidence is provided. In the next case, a patient is helped to understand her illness and its meaning; however, I know of no studies that tell us anything about the causes or meaning of panic attacks, except for epidemiological studies.

Any "psychiatric" paper submitted for publication would be refused if it made as many unsupported assertions. The *Journal* appears to have two sets of standards, one for psychoanalytic articles and another for psychiatric articles. Freud said psychoanalysis deals with illnesses of the soul. Psychiatry deals with illnesses of the mind. Freud said psychoanalysis is not a medical discipline and does not obey the laws of science that control medicine. Let psychoanalytic organizations promote psychoanalysis and let the American Psychiatric Association promote the medical specialty of psychiatry.

The conflict is there, but nobody dares talk about it.

HANS HUESS, M.D.
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SIR: The article by Drs. Perry, Cooper, and Michels asserted that one benefit of a psychodynamic formulation is to help guide all treatments. After developing three different psychodynamic formulations for Mr. A, the authors stated that all three formulations alert the therapist that difficulties will develop in the therapeutic relationship after a honeymoon period.

The summarizing statement was described by the authors as identifying the extent and quality of previous interpersonal relationships. Mr. A was described as having a lifelong tendency to annoy his superiors either by being obsequious or by challenging their authority. This history alerts the clinician to probable future behavior; the psychodynamic formulation attempts to explain the behavior. In short, the best predictor of future behavior is knowledge of past behavior obtained by a careful history, not a psychodynamic formulation that merely attempts to explain the past behavior.

RAY W. THWEATT, M.D.
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Dr. Perry and Colleagues Reply

Sir: Dr. Huessy calls attention to the distinction between meaning and cause. We agree that it is important to recognize this distinction. In fact, we indicated in our article (p. 544) the need to note nondynamic etiological factors, and we purposefully chose case examples (p. 545) in which possible biological determinants were pronounced. We did not state that the patients' depression, delusions, or panic attacks were caused by the meaning of these symptoms. Rather, we pointed out that an understanding of how the individual patient experiences these symptoms may help guide clinical management and that conveying this understanding in an empathic, timely, and appropriate manner may enhance the therapeutic alliance and increase compliance.

Although we also agree that the criteria used to demonstrate meaning and cause are different, we do not agree with Dr. Huessy's suggestion that the *Journal* stop publishing clinical papers that do not report the results of systematic research. The issue is not "psychoanalytic" versus "psychiatric" articles but whether the profession is interested in a spectrum of topics ranging from case reports to laboratory research (each with its appropriate standards for evidence) or is interested in only a small segment of that spectrum.

Finally, we note that Dr. Huessy has learned an unfortunate lesson from some psychoanalysts: selecting a specific citation from Freud to buttress an argument while ignoring many passages that would suggest a quite different reading.

Dr. Thweatt points out that a psychodynamic formulation is, ultimately, a description of patterns of past behavior. We agree! Its value is in conceptualizing and crystalizing those patterns, thereby allowing a broader array of predictions.

SAMUEL PERRY, M.D.
ARNOLD COOPER, M.D.
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New York, N.Y.

Nocturnal Coprolalia and Phonic Tics

Sir: Tourette's disorder has been associated primarily with symptoms that occur during the waking hours. Only recently have nocturnal problems been observed. Somnambulism, increased nighttime awakenings, and motor and phonic tics that occur during sleep have been reported in about 50% of Tourette's disorder patients (1, 2).

We recently evaluated a 9-year-old boy who met the *DSM-III-R* criteria for Tourette's disorder and also evidenced nocturnal coprolalia and other vocal tics. His mother reported that during a sound sleep he would frequently spasmodically utter "fuck," "fuck face," or other obscenities. She reported a waxing and waning pattern of other phonic tics during apparently sound sleep, including peacock-like "bird calls," without motor tics. On various occasions the boy would sit upright in bed with his eyes open and display both motor and vocal tics; he would then return to sleep. He did not respond when his name was called during these episodes and did not remember these events in the morning. He evidenced similar multiple motor and phonic tics with coprolalia when awake.

These unusual paroxysmal episodes of motor and phonic tics while the boy was sitting up with his eyes open may represent arousals from stage 3 or 4 deep sleep, since the episodes were stereotypic, the patient was unresponsive to environmental intrusion, and he did not remember the episodes the next day (2). In the absence of sleep studies it cannot be ascertained at what level(s) of sleep this youngster's exclusively phonic tics occurred. The selective expression of phonic tics, rather than combined phonic and motor tics, as a function of state of sleep may reflect unknown neurophysiologic correlates in this patient. The presence of tics during his paroxysmal arousal states may be related to the stereotypic quality of such arousal events in individuals without tics.

It has been suggested that tics disappear during sleep (*DSM-III*, p. 74). In our population of 115 patients with Tourette's disorder, at least eight have had motor or phonic tics while asleep. This was our first experience with nocturnal coprolalia.

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LARRY BURD, M.S.
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Defining Late Luteal Phase Dysphoric Disorder

Sir: I read with interest the article "Treatment of a Patient With Seasonal Premenstrual Syndrome" by Barbara L. Parry, M.D., and colleagues (1), particularly because of its focus on a biological rhythms approach to understanding women. However, I would like to give a word of caution to psychiatrists and other mental health workers who will now be educating themselves about late luteal phase dysphoric disorder, which appears in appendix A of *DSM-III-R*. Dr. Parry and associates, in their opening sentence, implied that premenstrual syndrome and late luteal phase dysphoric disorder are synonymous. They are not!

We must not reify women's fears that psychiatrists are labeling women—in particular, those with premenstrual syndrome—as mentally ill. Which diagnosis did the authors establish: premenstrual syndrome or late luteal phase dysphoric disorder? While all women with the latter have premenstrual syndrome, not all women with premenstrual syndrome have late luteal phase dysphoric disorder. What criteria did the authors use to make the diagnosis?

At a time when psychiatry is making progress in defining this specific subset of a syndrome, we need to be especially careful that the use of this label is clearly delineated and appropriately restrictive.

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SALLY K. SEVERINO, M.D.
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Dr. Parry and Associates Reply

SIR: We thank Dr. Severino for her letter. Unfortunately, much confusion surrounds the nosology of the historically designated term "premenstrual syndrome," more recently defined as late luteal phase dysphoric disorder.

It is our understanding that the term "late luteal phase dysphoric disorder" was developed to delineate diagnostic criteria for what has previously been referred to as premenstrual syndrome. There has been no consistently agreed-upon definition for premenstrual syndrome; thus, we do not view it and late luteal phase dysphoric disorder as separate diagnostic categories with interfacing boundaries. Rather, we feel "late luteal phase dysphoric disorder" is a more specific term which delineates the nature, timing, and severity of premenstrual symptoms that meet criteria for a disorder.

Our patient had severe premenstrual affective symptoms, which we documented by daily ratings, weekly mood inventories, and Hamilton Rating Scale for Depression scores over a 3-year period. The affective nature of our patient's symptoms, their temporal relationship to the menstrual cycle, and their severity met the criteria for late luteal phase dysphoric disorder. We felt that this patient's condition was a disorder because premenstrually she developed suicidal depressions which markedly interfered with her adaptive functioning at work and at home.

Our attempt was not to delineate a new diagnostic entity but rather to describe clinically and scientifically a patient with a seasonal form of a recurrent premenstrual (late luteal) dysphoric disorder. To our knowledge, similar patients have not been described. At the time of submission of our manuscript, the term "late luteal phase dysphoric disorder" had recently been approved for inclusion in appendix A of *DSM-III-R*. By using "late luteal phase dysphoric disorder" in association with "premenstrual syndrome," we wished to familiarize our readers with this terminology. Our intent was to educate and, as a result, to help diminish the multitude of misinterpretations already generated by this disorder. It would be unfortunate if, after the attempt to delineate the amorphous premenstrual syndrome with well-defined diagnostic criteria, misunderstandings regarding nomenclature interfered with clinical descriptions and further explorations into the nature and treatment of this condition.

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Redefining Psychiatry

SIR: Hurrah for Dr. Thomas Detre's commentary on the future of psychiatry (1)! Psychiatry has indeed been living in an intellectual Disneyland (to spare the hurt feelings of analysts?). This neglect of our duty contributes to our colleagues' skepticism, everyone's confusion, and the public's gullibility. Shirley MacLaine's ideas about UFOs and "past lives" share talk-show time with the ideas of scientists and clinicians. Any idea can be called "new-age" and become "therapy." Schizophrenia is still called a "functional" psychosis (so neurologists don't have to treat it?) despite all the evidence of its organic nature. Let's support Dr. Detre and others in rethinking our perspectives and practices. There will be no easy path in the uncertain and overlapping zones between biological CNS dysfunction and spiritual-philosophical "problems in living," but we do have to try.

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Use of ECT in the United States

SIR: In a recent survey of the use of ECT in the United States in 1975 and 1980 (1), James W. Thompson, M.D., and Jack D. Blaine, M.D., concluded, "In agreement with most of the literature, our data indicate that the use of ECT is decreasing." Their estimates were based on the data of the Sample Survey Program of the National Institute of Mental Health (NIMH), which they presumed is a representative sample of institutional practice. I believe that they underestimated the use of ECT and that their projection was inaccurate.

The first major survey of national use of ECT was undertaken in 1976 by the American Psychiatric Association's Task Force on Electroconvulsive Therapy (2). Using self-reports by a randomly selected sample of 20% of the members of the Association, the task force estimated annual use at 4.4/10,000 population. This estimate is comparable to estimates in other national surveys: 2.99/10,000 in Canada in 1979, 3.53/10,000 in Great Britain in 1980, and 5.3/10,000 in Ireland in 1982 (3). The Thompson and Blaine estimates for U.S. use were lower: 2.8/10,000 in 1975 and 1.6/10,000 in 1980. They reported a decline in the use of ECT in various facilities except public general hospitals, where use of ECT actually increased. The earlier national reports were based on practitioner surveys, while Drs. Thompson and Blaine relied on reports from a sample of institutions. In another institutional survey in 1976, use of ECT varied; it was used for less than 2% of patients admitted to public (state and Veterans Administration) psychiatric hospitals, for 6%–12% of those admitted to academic-affiliated general hospitals, and for more than 20% of patients in private for-profit hospitals (4). In estimating use among institutions, weighting of representative samples is necessary to account for this wide disparity.

Other indicators of the use of ECT show an increasing interest during this decade. For example, the development of new instruments for ECT in Great Britain and by four manufacturers in the United States reflects an increased willingness to invest in what must be perceived as a growing market.

A better estimate, however, is in the number of citations about convulsive therapy in the scientific literature, which has been increasing, most dramatically since 1980 (3). Indexing of medical articles for electronic scanning by the National Library of Medicine began in 1966. In the first decade the average number of citations in MEDLINE indexed under terms equivalent to "electroconvulsive therapy" and "electroconvulsive shock" was 130 per year. In the second decade the number increased to 170 per year, with a minimum of about 120 per year between 1973 and 1975. Since then, the number has increased each year, and for 1984–1986 it rose to 210 per year. To these citations should be added those in the new journal *Convulsive Therapy,* which provided 31 reports in 1985 and 46 in 1986, increasing the annual totals to more than 230 in 1985 and 270 in 1986.

The survey of Drs. Thompson and Blaine is a lagging indicator of interest in and use of ECT, and it may also suffer from sampling error. Other research indicates that the use and practice of ECT are increasing in this decade, accompanying the growing awareness that the treatment is an integral part of present psychiatric practice.

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MAX FINK, M.D.
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Drs. Thompson and Blaine Reply

SIR: Although our data show a decrease in the use of ECT in the United States between 1970 and 1980, we do agree with Dr. Fink that there has recently been increased interest in this treatment modality. This new interest has taken many forms, including several new research projects and the NIH/NIMH Consensus Development Conference on ECT in June 1985. We applaud this renewed interest in understanding the basic science, clinical, and service delivery aspects of ECT, since we feel strongly that it is important to base the use of medical treatments, as well as health policy formulation, on empirical, not ideological, criteria.

Dr. Fink also correctly observes that our data covered only the period from 1970 to 1980. As we noted in the paper, the use of ECT since 1980 may indeed have been increasing, although we would disagree that there are definitive data to show this at present.

We look forward to future research in this field and would argue that research questions on services are among the most important to be examined.

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Spontaneous Remission of MAOI-Induced Anorgasmia

SIR: I should like to offer an alternative explanation for the findings reported by H. George Nurnberg, M.D., and Philip E. Levine, M.D., in their article "Spontaneous Remission of MAOI-Induced Anorgasmia" (1). The authors suggested that "an integrated shift in CNS functioning" may have accounted for the return of normal orgasmic response in patients who initially developed anorgasmia as a side effect of treatment with monoamine oxidase inhibitors (MAOIs). However, it is also possible that some, if not all, of these patients changed their sexual techniques to accommodate the higher orgasmic threshold produced by their medication. It has been my experience as a psychologist specializing in the treatment of sexual dysfunction that MAOIs do not so much abolish the orgasmic response as make it much more difficult to achieve. Patients encouraged to undertake more prolonged and intense sexual stimulation are usually able to compensate for the orgasm-inhibiting effect of the medication. No doubt many patients taking MAOIs discover this on their own without the benefit of sex therapy. I have seen one patient for whom this was certainly the case: a young woman who presented with the unusual complaint of premature orgasm, a symptom she had developed when she stopped taking phenelzine but continued the more intense sexual stimulation she had begun while taking the medication. In general, research on the spontaneous remission of sexual dysfunctions suggests that most cases are in fact self-cures rather than truly unprovoked occurrences (2).

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Drs. Levine and Nurnberg Reply

SIR: We appreciate Dr. Nathan's response to our paper, which adds support for the clinical wisdom of assuming a conservative approach when patients develop MAOI-induced anorgasmia but must continue their medication to prevent a relapse of their symptoms. Dr. Nathan's observation regarding the possibility of patients attaining orgasm by increasing the intensity of precoital stimulation provides the clinician with an alternative approach for guiding patients who are concerned about their sexual dysfunction. However, this position suggests caution because the premise of an elevated orgasmic threshold is potentially nonfalsifiable and might place disproportionate responsibility on the patient to continue trying harder. Alternatively, it is likely that when the physician counsels the patient to accept and not be alarmed by the medication-induced anorgasmia, a reduction in the anxiety-induced sexual inhibition also potentiates the lowering of the orgasmic threshold. Kaplan (1) emphasized the role of "distracting the inhibitor" when dealing with anorgasmic patients. Thus, we do not disagree with Dr. Nathan's premise that active behavioral interventions could be helpful with these patients but find that our clinical experience still supports the latter approach.

At the same time, we feel that truly spontaneous remissions probably do occur. Our basic understanding of the suggested potent effects of behavior modification or cognitive refocusing as well as our understanding of the effects of medications like MAOIs would be greatly enhanced if the CNS and peripheral correlates of the human sexual response were understood better. Our observations suggest the possibility of homeostatic physiological processes that play a role in the restoration of normal sexual functioning after MAOI-induced anorgasmia. The close association in our patients between the onset of anorgasmia and the initiation of a good therapeutic response hints at some integrated effect of the medication on both the affective disorder and orgasmic potential. Understanding both the initial and longer-term effects of MAOIs on neurotransmitter levels, receptor sensitivity and quantity, and other CNS components might shed light on the underlying mechanisms of depression as well as the sexual response. Beyond alerting clinicians to the feasibility of continuing MAOIs even in the presence of disturbing sexual dysfunction, the purpose of our paper was to highlight an area where our understanding is inadequate. More study is clearly indicated.

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Psychodynamic Therapy With Borderline Patients

SIR: Dr. Robert J. Waldinger is to be congratulated for his heroic effort to summarize some of the controversial views about intensive psychodynamic psychotherapy with borderline patients (1). I would like to thank him for reporting correctly some aspects of my viewpoint and, at the same time, correct some misstatements. These may derive from the fact that he focused on two of my earlier publications and did not have the benefit of the four that followed in the next 10 years (2–5).

The original notion of etiology was later altered to include 1) genetic and constitutional factors along with maternal libidinal unavailability for separation-individuation and 2) later intrapsychic elaboration of these events. The borderline patient at the outset of treatment relates not by transference but by transference acting out; i.e., he or she projects self and/or object representations with their associated affects on the therapist without any awareness of the therapist's independent existence. Confrontation of the transference acting out helps the patient to convert transference acting out into therapeutic alliance and transference, at which point the patient is able to use interpretations. Confrontation and the neutrality of the therapist also provide soothing and holding functions.

Communicative matching does not include self-disclosure but, rather, discussing the patient's interests with him or her. Dr. Waldinger read my view as "creating a better parenting experience." Nothing could be further from my view. I have always stressed the importance of the therapist's objectivity and neutrality to serve as a framework for the development of the therapeutic alliance and transference and for working through the depression by means of interpretation. Both positive and negative transferences eventually must be interpreted and worked through. If there have been failures that produce developmental arrests, the painful affects of the abandonment depression have to be worked through before the patient can overcome the arrest.

The article seems to cast a negative shadow on the borderline patient; i.e., the treatment is arduous, and the patients are difficult to engage and do not complete therapy. My colleagues and I have not found this view to be true. Most of our patients do engage and do complete. Could it be that the patient is being blamed for the therapist's difficulties?

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JAMES F. MASTERSON, M.D.
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Dr. Waldinger Replies

SIR: I appreciate Dr. Masterson's response to my discussion of his work on dynamic psychotherapy with borderline patients. Several points about that discussion are worth clarifying.

I did indeed have the benefit of Dr. Masterson's later work when I prepared my article, including the four books that he cites in his letter. I did not cite these later works because his modification of earlier ideas about etiology did not appear to result in any fundamental change in his therapeutic technique.

Dr. Masterson's discussion of his ideas about communicative matching was instructive. To the extent that he has described the technique as "discussing with the patient from my own knowledge general and universal aspects of [a] particular new interest or feeling presented" (1), there is room to infer that this involves self-disclosure. As this was not what Dr. Masterson intended, readers will find the clarification useful.

Although Dr. Masterson writes that he in no way aims to create a better parenting experience for borderline patients, he has explicitly stated in one of his later works that by using communicative matching, the therapist "compensates for the defect left by the mother's withdrawal and fuels and invigorates the patient's individuation" (2). This does not imply a lack of objectivity on the part of the therapist, but it does suggest the provision of an experience designed to make up for parental deficits.

Dr. Masterson raises two more fundamental issues. I find perplexing his statement that, in his experience, borderline individuals generally do engage in and complete treatment. This places him squarely at odds with available empirical evidence, including a survey by John G. Gunderson, M.D., and myself of experts in this area (3) as well as other recent research (4). I wonder if this discrepancy is due to different patient populations studied. For example, many of the patients discussed at length in Dr. Masterson's *Psychotherapy of the Borderline Adult* (1) appear to be on the less dysfunctional end of the spectrum of borderline disorders. I do not know whether these patients would meet the current restrictive *DSM-III* criteria for borderline personality disorder.

Finally, Dr. Masterson writes that in labeling the treatment of borderline patients as "arduous" I cast a "negative shadow" on patients and blamed them for the difficulties of their therapists. I meant to do no such thing. My experience is that the early stages of intensive psychotherapy with borderline patients can be at least as arduous for the patient as for the therapist and that the work demands considerable energy and persistence from both parties.

Just as it is important to avoid blaming patients for their difficulties, so is it important to avoid blaming therapists. If we do not openly acknowledge the problems inherent in treating patients with borderline personality disorder, we risk leaving therapists with undue burdens of guilt when the work does not go smoothly.

Were treatment more straightforward, I suspect that "heroic" efforts would not be required to summarize controversies in the field.

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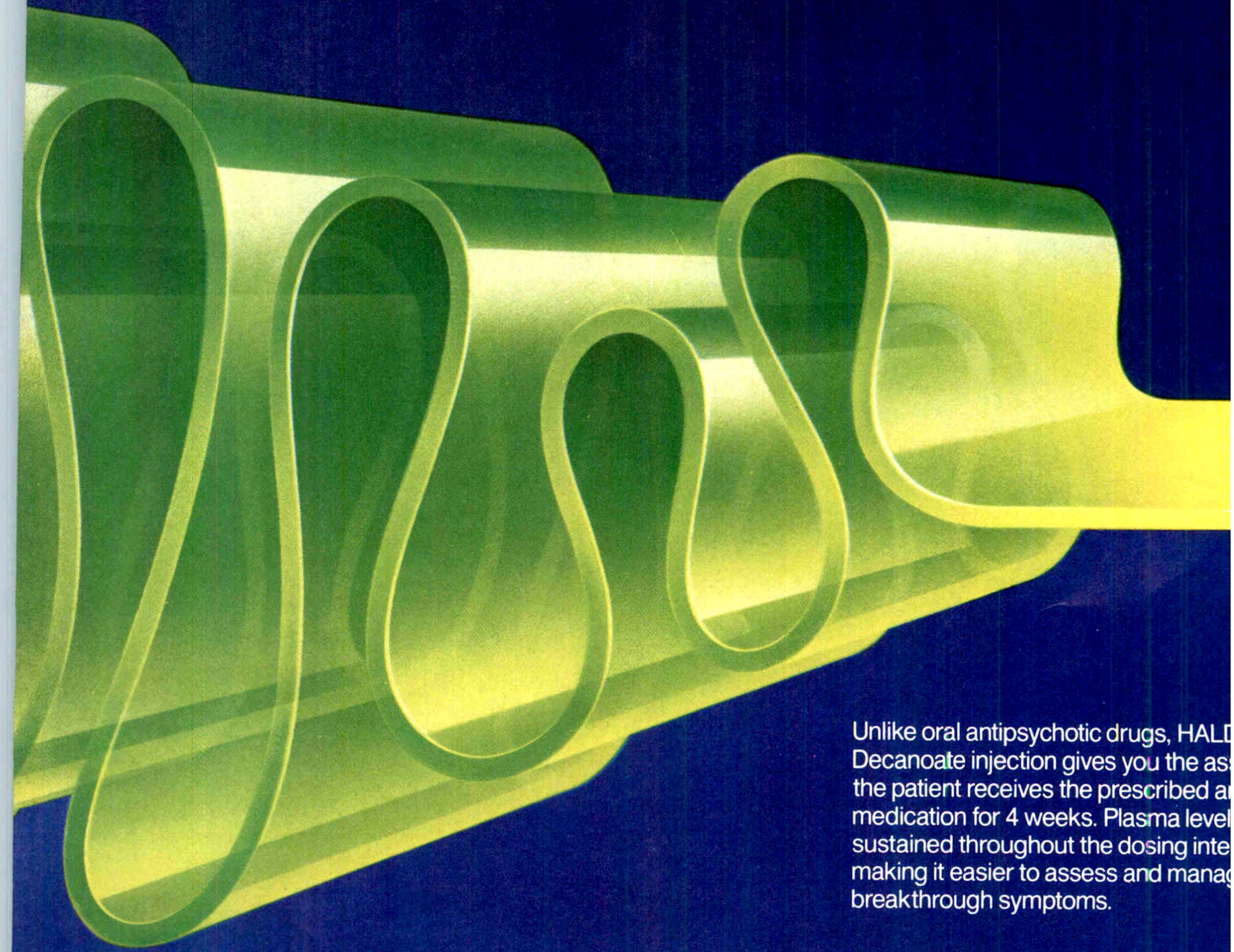

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References

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Please see brief summary of prescribing information on next page.

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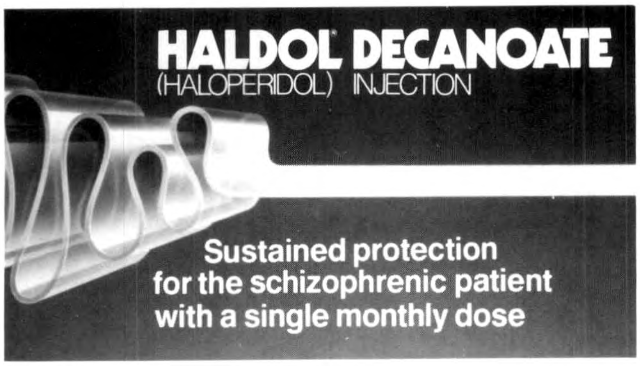

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

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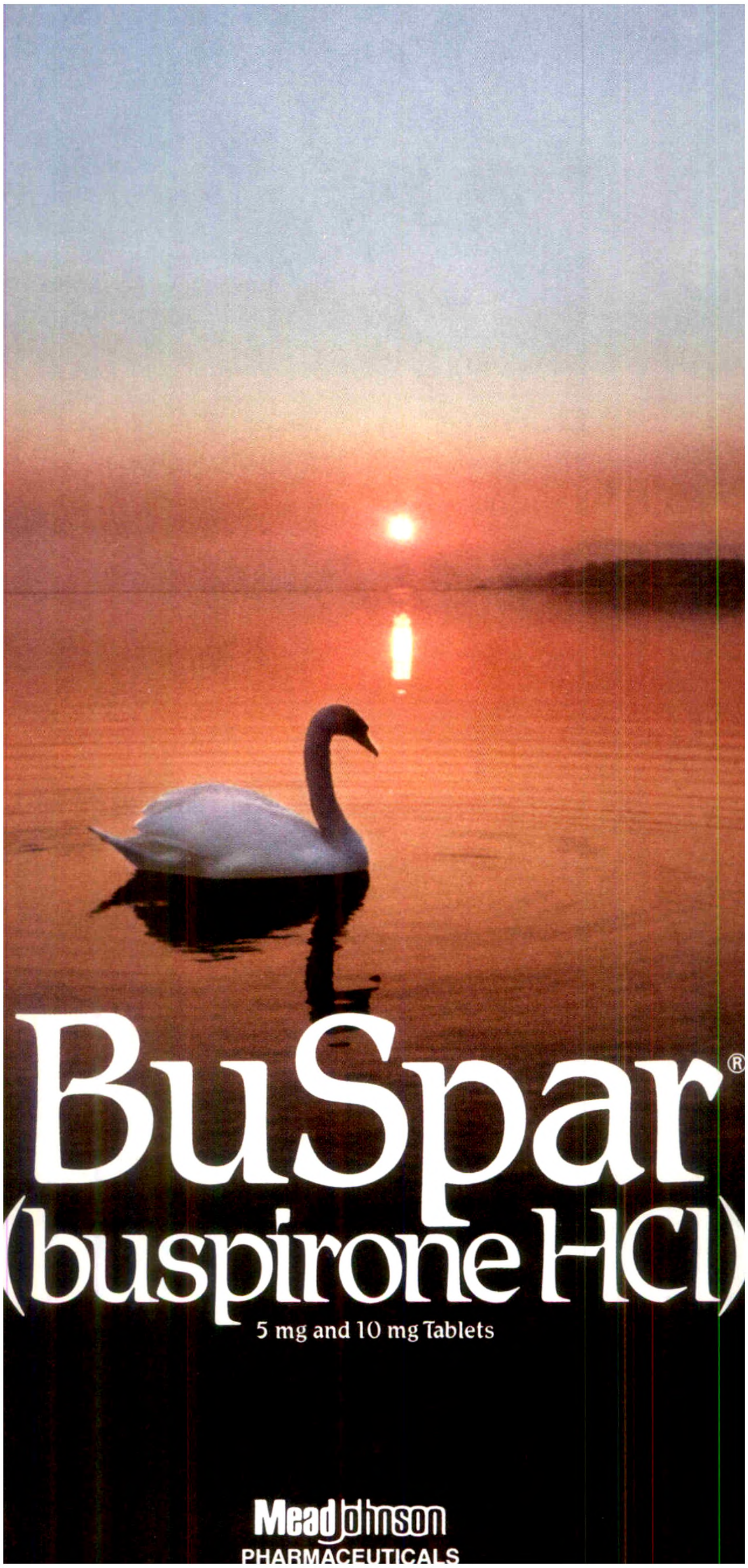

BuSpar®
(buspirone HCl)
5 mg and 10 mg Tablets

Mead Johnson
PHARMACEUTICALS

BuSpar® (buspirone HCl) 5 mg and 10 mg Tablets

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, light-headedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, light-headed feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2% *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1% *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin.* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows. Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension, rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent, dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion, infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis, rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent. flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare: burning of the tongue *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion, rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido, rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior)

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative

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Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information about the characteristics and personal history of patients.

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Papers submitted with the request for prompt publication must meet stringent criteria of originality and be of major, immediate importance. Authors must state their reasons for wanting prompt publication in a cover letter to the Editor. These papers are given priority in scheduling; however, authors should be aware that the minimum publication time is 4 months. (This policy is automatic for all Clinical and Research Reports.)

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients should include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

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Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

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These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including a précis of no more than 100 words, tables, and figures) and may not include more than 100 references.

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The only difference between these two types of papers is length. **Regular Articles** contain no more than 3,800 words, including a précis of no more than 100 words, references, tables, and figures. **Brief Communications** contain no more than 2,500 words, including a précis of no more than 100 words, references, tables, and figures. (A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words.) Articles that exceed 3,800 words will be returned unreviewed to the authors.

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A prompt publication policy (i.e., publication within 4 to 6 months after acceptance) is in effect for Clinical and Research Reports. Manuscripts may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including a précis of no more than 40 words, text, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

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The number of words, tables, and figures in the paper and the telephone number of the corresponding author should be typed in the upper right-hand corner of the title page. At least three key words that describe the content of the paper should be typed in the lower right corner of the page.

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Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3$, 17, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

Tables and Figures

The *Journal* does not publish tables or figures that have appeared in other English-language publications. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables. Tables are reserved for presentation of numerical data and should not be used as lists or charts. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given. **Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines.**

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Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

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2. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
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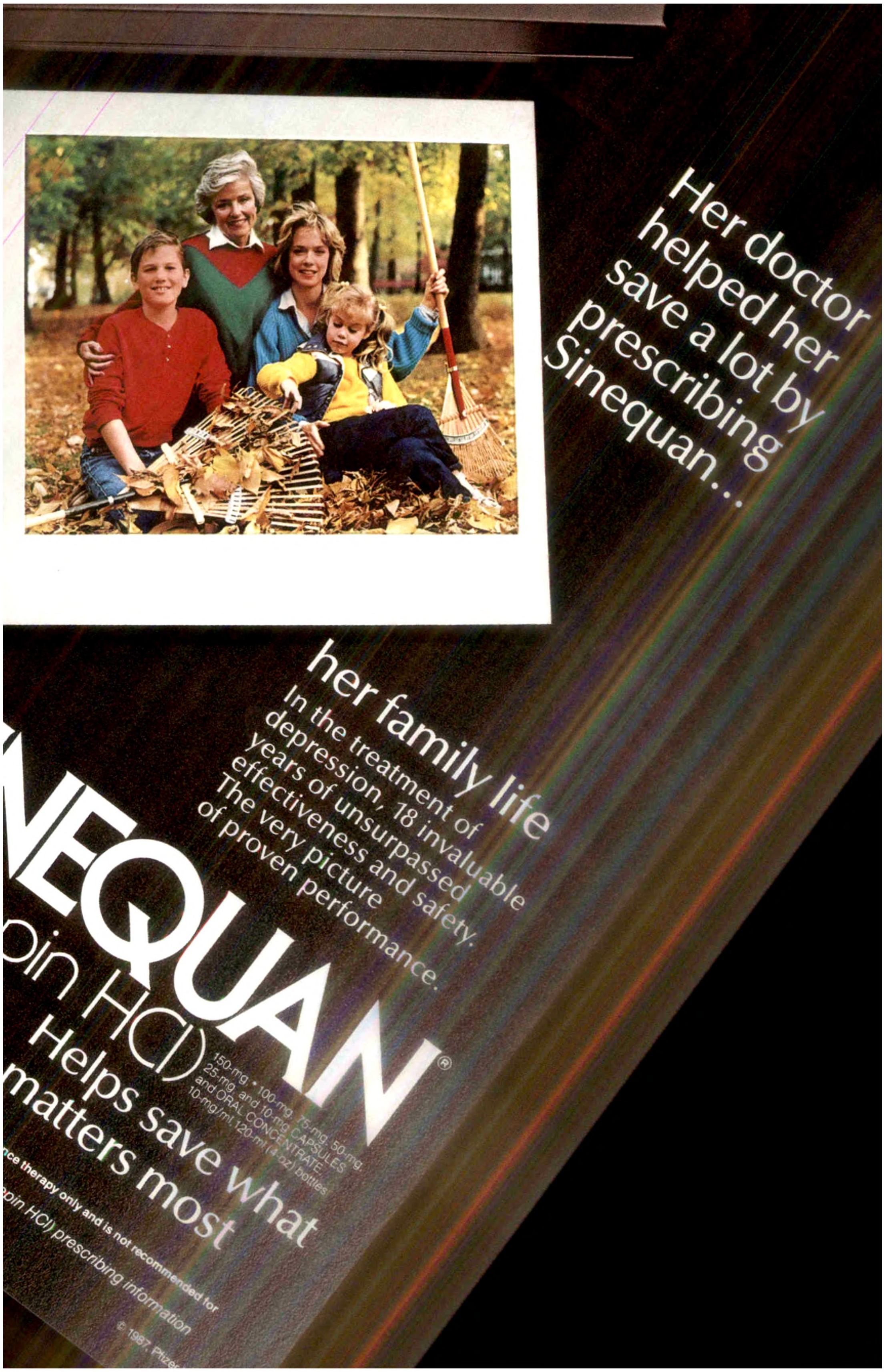

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BRIEF SUMMARY
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Indications. SINEQUAN is recommended for the treatment of:

1 Psychoneurotic patients with depression and/or anxiety.

2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol).

3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly)

4. Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN (doxepin HCl) administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.

2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.

2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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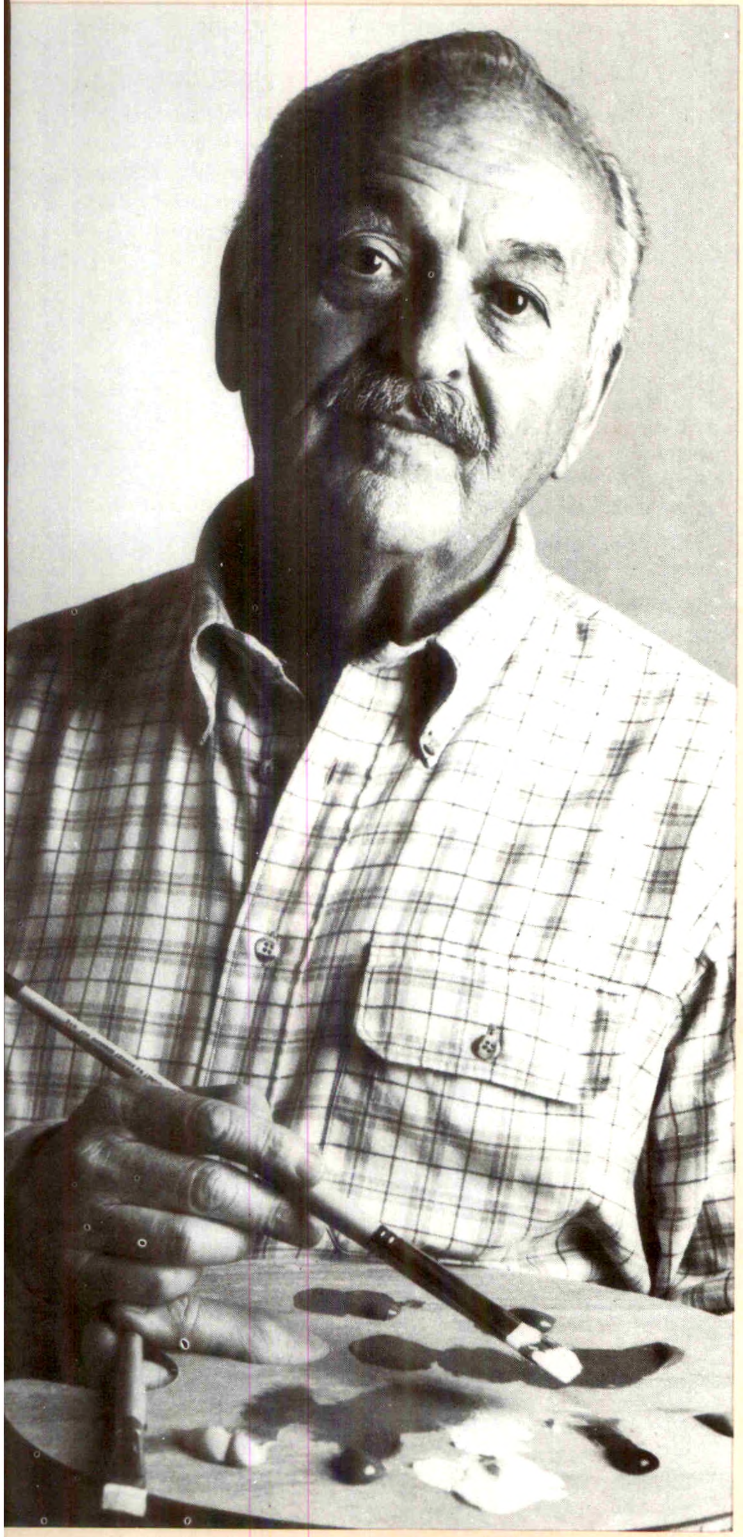

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The efficacy and safety of MOBAN was recently demonstrated in a violent geriatric patient with delusional thinking and paranoid ideation. Taken to a hospital by force, the patient had assaulted his bedridden wife because he believed she was having an affair with a younger man.

Results:

- Admitted as an involuntary patient, MOBAN succeeded in reducing his symptoms sufficiently to permit transfer to a psychogeriatric ward after just five days of treatment.
- Dosage was subsequently reduced to only 15 mg/day.
- After four weeks, there was no evidence of delusional thinking, paranoia or hallucinatory behavior.
- Even without anticholinergic medication, there were no side effects.

Conclusion:

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INDICATIONS: MOBAN is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of MOBAN was established in clinical studies which enrolled newly hospitalized and chronically hospitalized, acutely ill, schizophrenic patients as subjects.

CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause, and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may supress or partially supress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic supression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceeding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

Concentrate: 20 mg/ml in 4 oz (120 ml) bottles.

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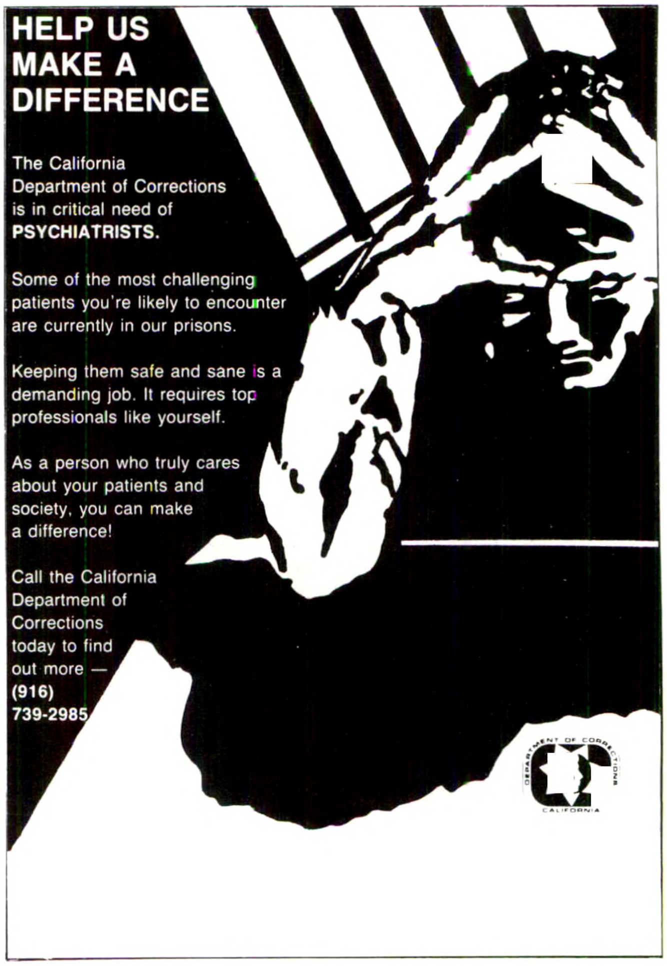

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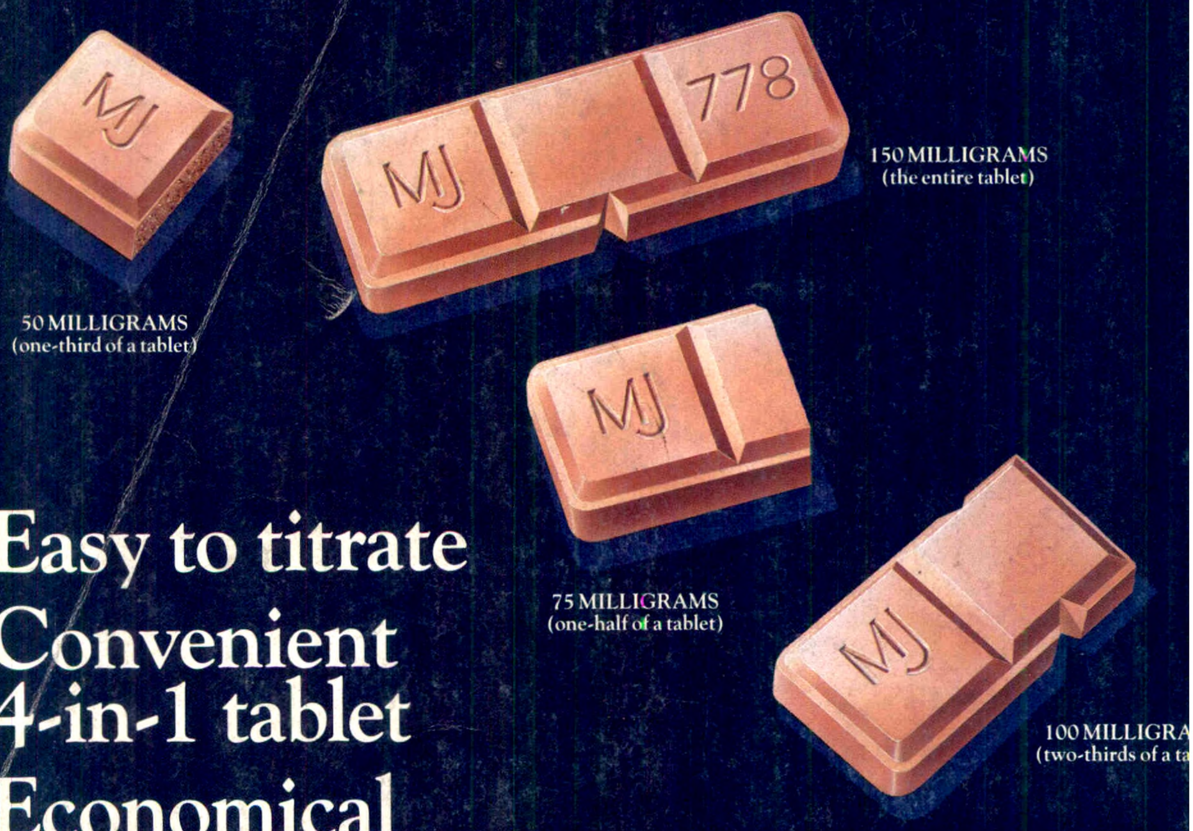

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 3 March 1988

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Toward Rational Pharmacotherapy for Posttraumatic Stress Disorder: An Interim Report

By Matthew J. Friedman

DSM-III Axis IV Revisited

By Joseph M. Rey, Gavin W. Stewart, Jon M. Plapp, et al.

Official Journal of the American Psychiatric Association

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Sunday, May 8

Opening Comments
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Los Angeles, California

Anxiety and Suicide
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Suicide and Other Consequences of Childhood and Adolescent Anxiety Disorders
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Hershey, Pennsylvania

Monday, May 9

Opening Comments
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Albert Einstein Medical Center
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Anxiety and Depression: A Common Neurobiological Substrate?
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National Institute of Mental Health
Bethesda, Maryland

Anxiety and Alcoholism
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College of Physicians and Surgeons of
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Tuesday, May 10

Opening Comments
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Anxiety and Sexual Dysfunction
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Anxiety and Physical Illness
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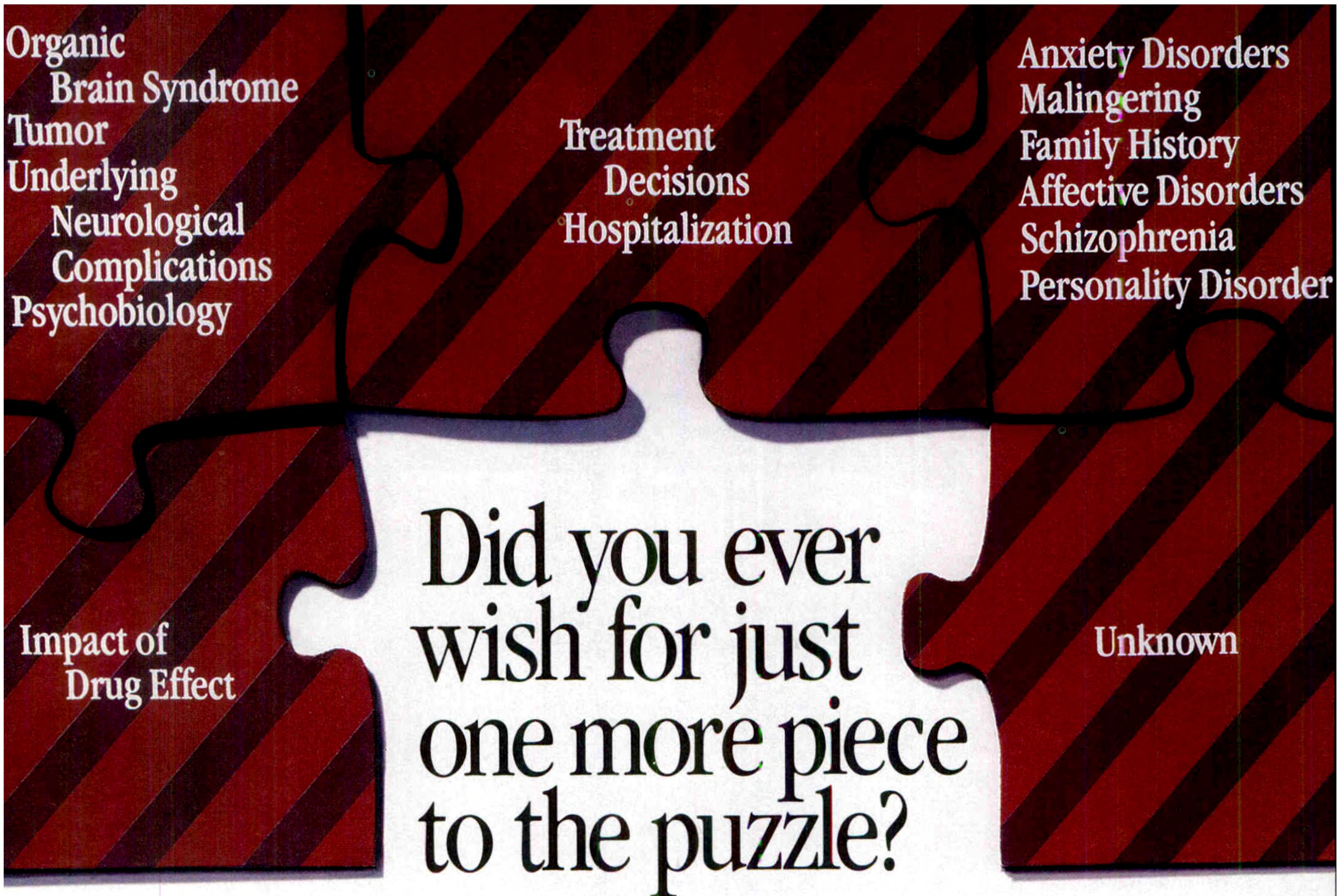

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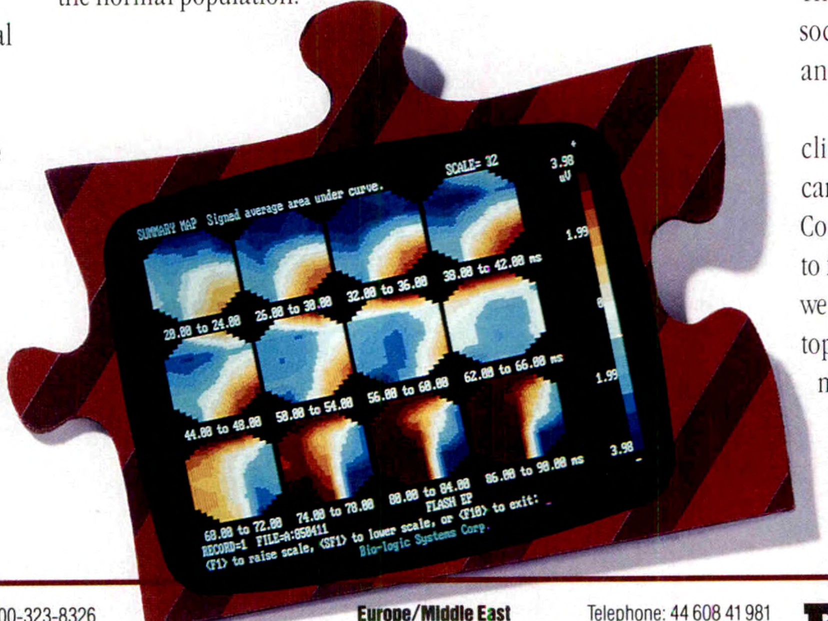

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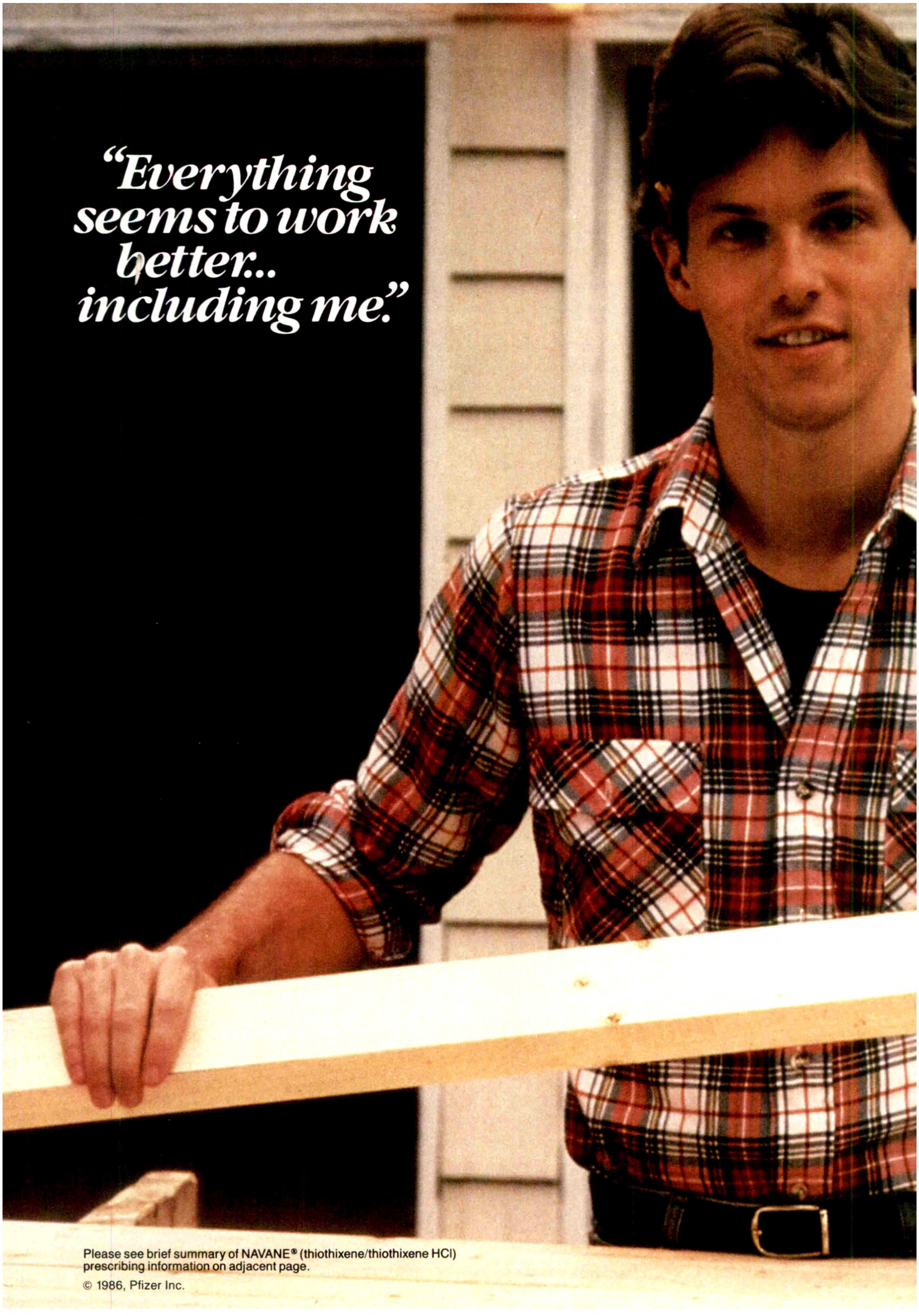
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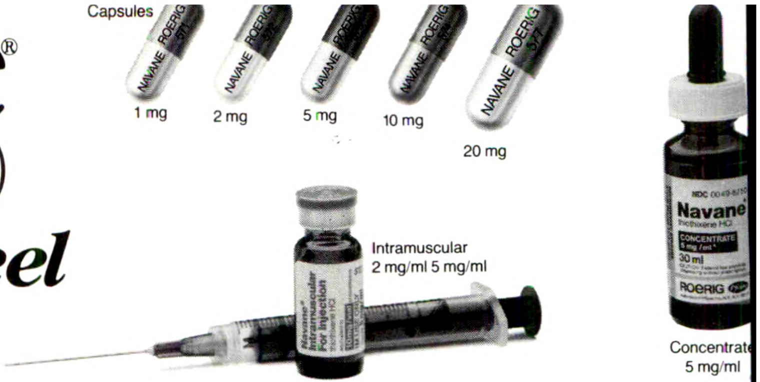

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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver da (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in pa on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular sho injected well within the body of a relatively large muscle. The preferred sites are the upper outer qu of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older childre then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary t avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. culture experiments indicate that approximately one third of human breast cancers are prolactin-depe *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patien a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gy mastia, and impotence have been reported, the clinical significance of elevated serum prolactin le unknown for most patients. An increase in mammary neoplasms has been found in rodents after c administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to however, have shown an association between chronic administration of these drugs and mammary t igenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neurolepti develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be gi possible, full information about this risk. The decision to inform patients and/or their guardians mu viously take into account the clinical circumstances and the competency of the patient to understa information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with N (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phe azines, all of the known side effects and toxicity associated with phenothiazine therapy should be bo mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hy sion occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of pressure may result. Nonspecific EKG changes have been observed in some patients receiving N (thiothixene). These changes are usually reversible and frequently disappear on continued Navane th The incidence of these changes is lower than that observed with some phenothiazines. The clinical s cance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuat Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothia but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with N infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospina abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been rep Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptom be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in patients on long-term therapy or may occur after drug therapy has been discontinued. The syndro characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrus tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be a panied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoi sis. It has been reported that fine vermicular movement of the tongue may be an early sign of the synd If this or any other presentation of the syndrome is observed, the clinician should consider possible d tinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient been infrequently observed in some patients. No clinically confirmed cases of jaundice attributa Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocy which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have be sociated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopeni

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis hav reported with Navane. Undue exposure to sunlight should be avoided. Although not experience Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tes necomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweati creased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazine been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appet weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenot therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WAR section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain ph azine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to of the cough reflex. In others, the cause could not be determined nor could it be established that dea due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full pres information.

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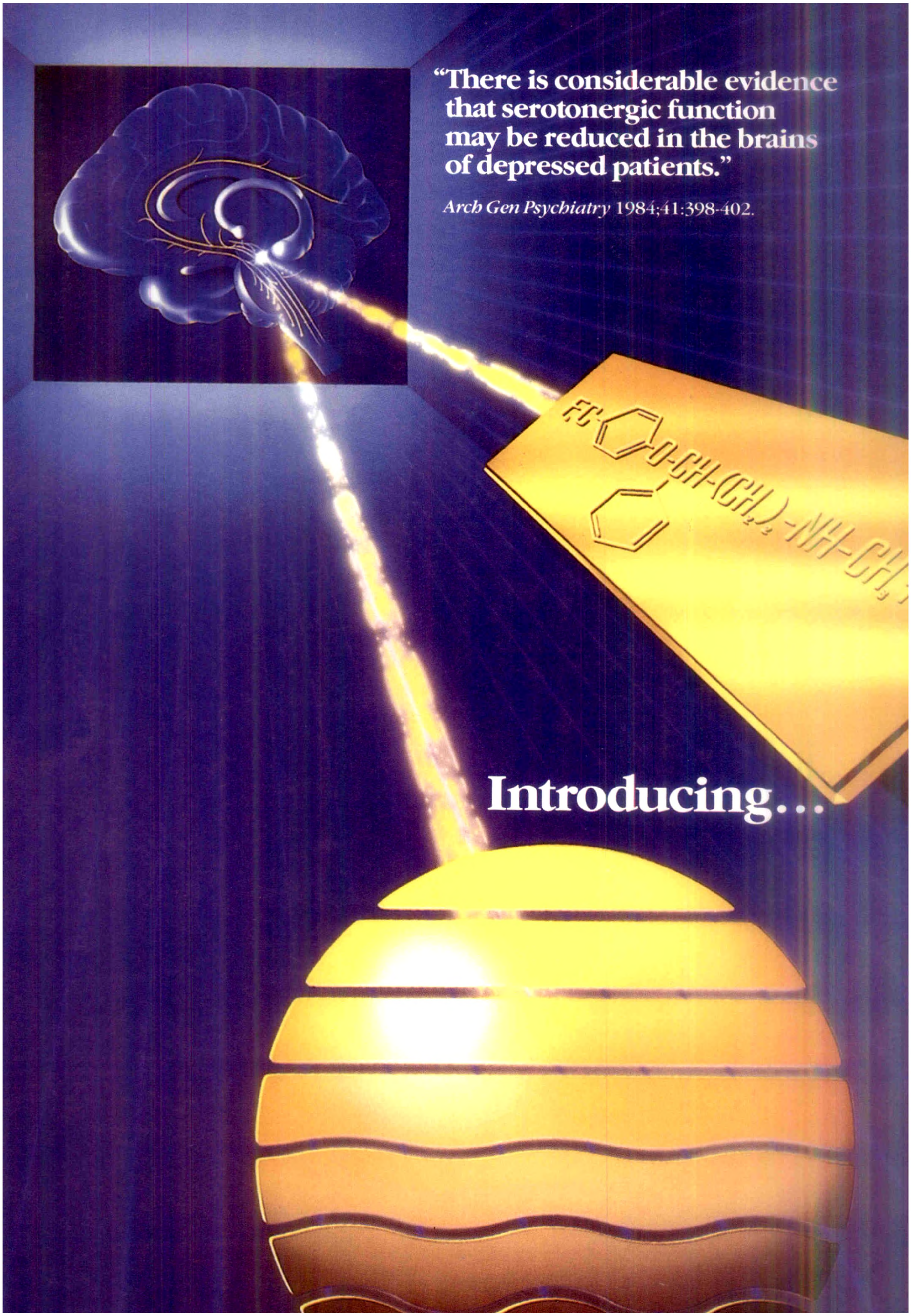

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Arch Gen Psychiatry 1984;41:398-402.

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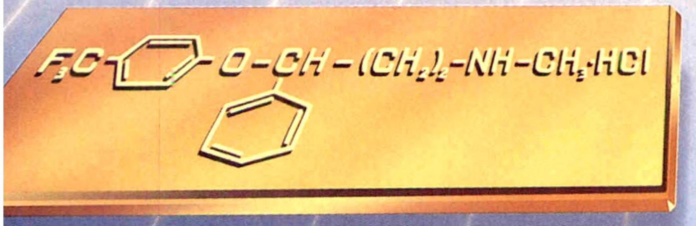

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fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Rash and Accompanying Events*—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

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*Events reported by at least 1% of Prozac patients are included
—Incidence less than 1%

Prozac® (fluoxetine

Other Events Observed During the Premarketing Evaluation of
During clinical testing in the US, multiple doses of Prozac were
tered to approximately 5,600 subjects. Untoward events associa
this exposure were recorded by clinical investigators using de
terminology of their own choosing. Consequently, it is not po
provide a meaningful estimate of the proportion of individuals exp
adverse events without first grouping similar types of untoward ev
a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictiona
nology has been used to classify reported adverse events. The fre
presented, therefore, represent the proportion of the 5,600
exposed individuals who experienced an event of the type cited o
one occasion while receiving Prozac. All reported events are
except those already listed in tables, those COSTART terms so gen
be uninformative, and those events where a drug cause was ren
important to emphasize that, although the events reported did occ
treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and
ated in order of decreasing frequency using the following de
frequent adverse events are defined as those occurring on one
occasions in at least 1/100 patients; infrequent adverse events
occurring in 1/100 to 1/1,000 patients; rare events are those occ
less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever,
edema, hangover effect, jaw pain, malaise, neck pain, neck rig
pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus,
mia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina pectoris, arrhythm
orrhage, hypertension, hypotension, migraine, postural hypotens
cope, and tachycardia; *Rare:* AV block (first-degree), brad
bundle-branch block, cerebral ischemia, myocardial infarct
bophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:*
stomatitis, dysphagia, eructation, esophagitis, gastritis, gingiviti
tis, liver function tests abnormal, melena, stomatitis, and thir
bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulc
itis, fecal incontinence, hematemesis, hepatitis, hepatomegal
chlorhydria, increased salivation, jaundice, liver tenderness
ulceration, salivary gland enlargement, stomach ulcer, tongu
oration, and tongue edema.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* goiter a
thyroidism.

Hemic and Lymphatic System—*Infrequent:* anemia and lymph
athy; *Rare:* bleeding time increased, blood dyscrasia, leukopen
phocytosis, petechia, purpura, sedimentation rate increased, an
bocythemia.

Metabolic and Nutritional—*Frequent:* weight loss; *Infrequen*
alized edema, hypoglycemia, peripheral edema, and weight ga
dehydration, gout, hypercholesteremia, hyperglycemia, hype
hypoglycemic reaction, hypokalemia, hyponatremia, and iron d
anemia.

Musculoskeletal System—*Infrequent:* arthritis, bone pain,
tenosynovitis, and twitching; *Rare:* bone necrosis, chondrody
muscle hemorrhage, myositis, osteoporosis, pathological fract
rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitatio
quent: abnormal gait, acute brain syndrome, akathisia, amnesia
ataxia, buccoglossal syndrome, CNS stimulation, convulsion, d
depersonalization, emotional lability, euphoria, hallucinations,
hyperkinesia, hypesthesia, incoordination, libido increased, ma
tion, neuralgia, neuropathy, paranoid reaction, psychosis, and
Rare: abnormal electroencephalogram, antisocial reaction, chro
syndrome, circumoral paresthesia, CNS depression, coma, dy
dystonia, extrapyramidal syndrome, hypertonia, hysteria, myocl
stagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent:* bronchitis, rhinitis, and yaw
quent: asthma, epistaxis, hiccup, hyperventilation, and pneumor
apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung
alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact de
dry skin, herpes simplex, maculopapular rash, and urticari
eczema, erythema multiforme, fungal dermatitis, herpes zoster, h
psoriasis, purpuric rash, pustular rash, seborrhea, skin discolorat
hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* amblyopia, conjunctivitis, ear
pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis,
corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, ir
sis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, ame
breast pain, cystitis, dysuria, fibrocystic breast, impotence, leu
menopause, menorrhagia, ovarian disorder, urinary incontinence
retention, urinary urgency, urination impaired, and vaginitis; *Ra*
tion, albuminuria, breast enlargement, dyspareunia, epididymiti
lactation, hematuria, hypomenorrhea, kidney calculus, metr
orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral
thritis, urinary tract disorder, urolithiasis, uterine hemorrhage
spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there
deaths among approximately 38 reports of acute overdose with fl
either alone or in combination with other drugs and/or alcohol.
involved a combined overdose with approximately 1,800 mg of
and an undetermined amount of maprotiline. Plasma concentr
fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respe
second death involved three drugs yielding plasma concentr
follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; code
mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxeti
enced two grand mal seizures that remitted spontaneously withou
anticonvulsant treatment (*see* Management subsection). T
amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involvi
fluoxetine doses. Other prominent symptoms of overdose inclu
tion, restlessness, hypomania, and other signs of CNS excitati
for the two deaths noted above, all other overdose cases recover
residua.

PV 2150 DPP

Prozac* (fluoxetine
hydrochloride, Dista)

Additional information available to the profession on request from

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NEW HORIZONS IN PSYCHIATRIC RESEARCH

DE NOUVEAUX HORIZONS S'OUVRENT À LA RECHERCHE PSYCHIATRIQUE

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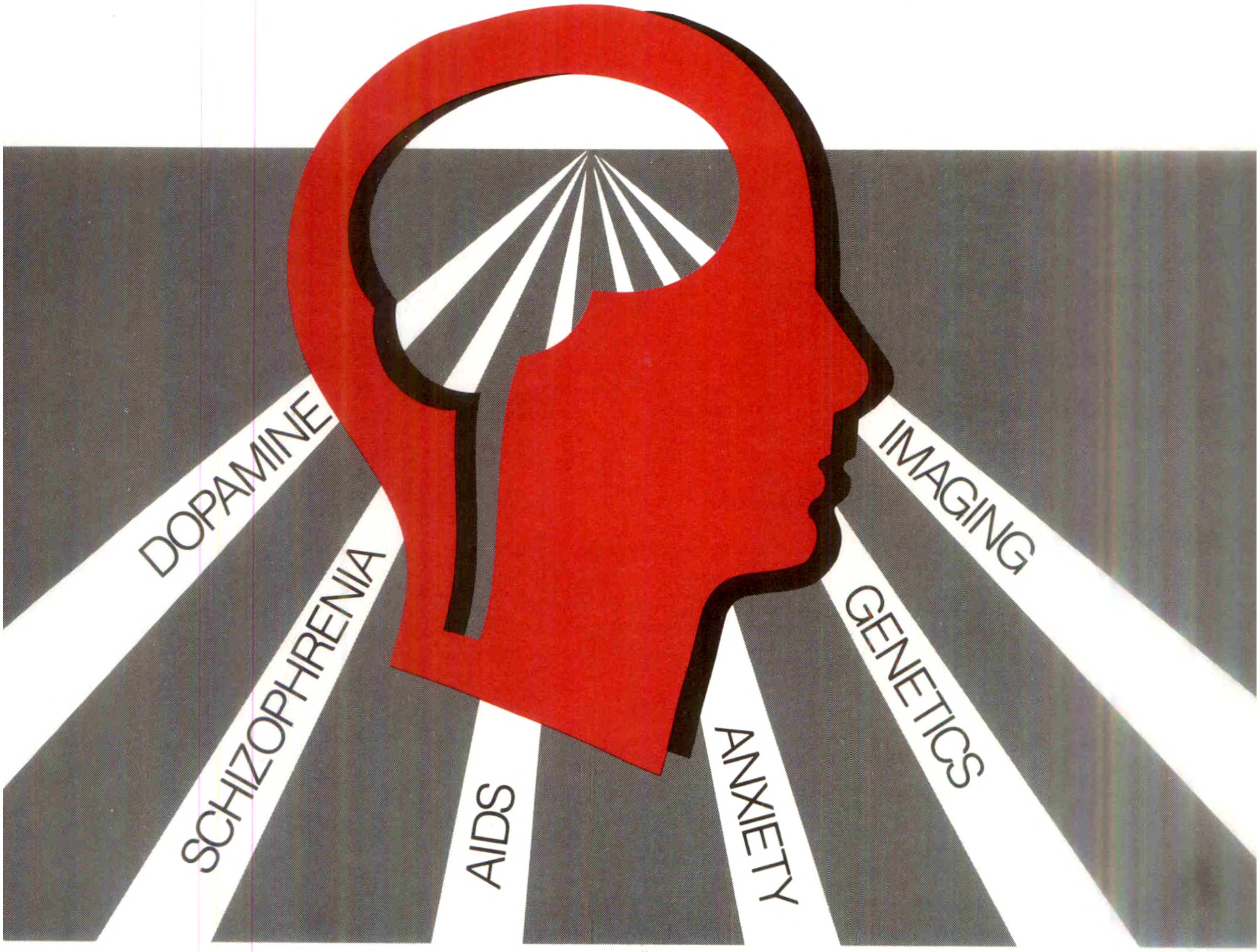

Symposium Overview
Herbert Pardes, MD, Moderator
Director, New York Psychiatric Institute
Professor and Chairman, Department of Psychiatry
Columbia University, College of Physicians and Surgeons
New York, NY

Psychiatric Aspects of AIDS
Frederick K. Goodwin, MD
Director, Intramural Research
National Institute of Mental Health
Bethesda, MD

A New Look at the Old Dopamine Hypothesis
Daniel R. Weinberger, MD
Chief, Clinical Brain Disorder Branch
National Institute of Mental Health
Washington, DC

New Horizons for Genetics and Mental Illness
Nancy S. Wexler, PhD
Associate Professor of Clinical Neuropsychology
Columbia University, College of Physicians and Surgeons
New York, NY

Neurobiological Mechanisms of Human Anxiety
Dennis S. Charney, MD
Director of Clinical Neuroscience Research Unit
Connecticut Mental Health Center
Associate Professor of Psychiatry
Yale University
New Haven, CT

Clinical Applications of Brain Imaging in Psychopharmacology
Monte S. Buchsbaum, MD
Professor of Psychiatry
Department of Psychiatry and Human Behavior
University of California, Irvine
Irvine, CA

CME Credit: The American Psychiatric Association designates this continuing medical education activity for 3 credit hours in Category I of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.

TUESDAY, MAY 10, 7:00—10:00 PM **GRAND SALON, HOTEL MERIDIEN**

A buffet will be served before the symposium—BIENVENUE À MONTRÉAL!

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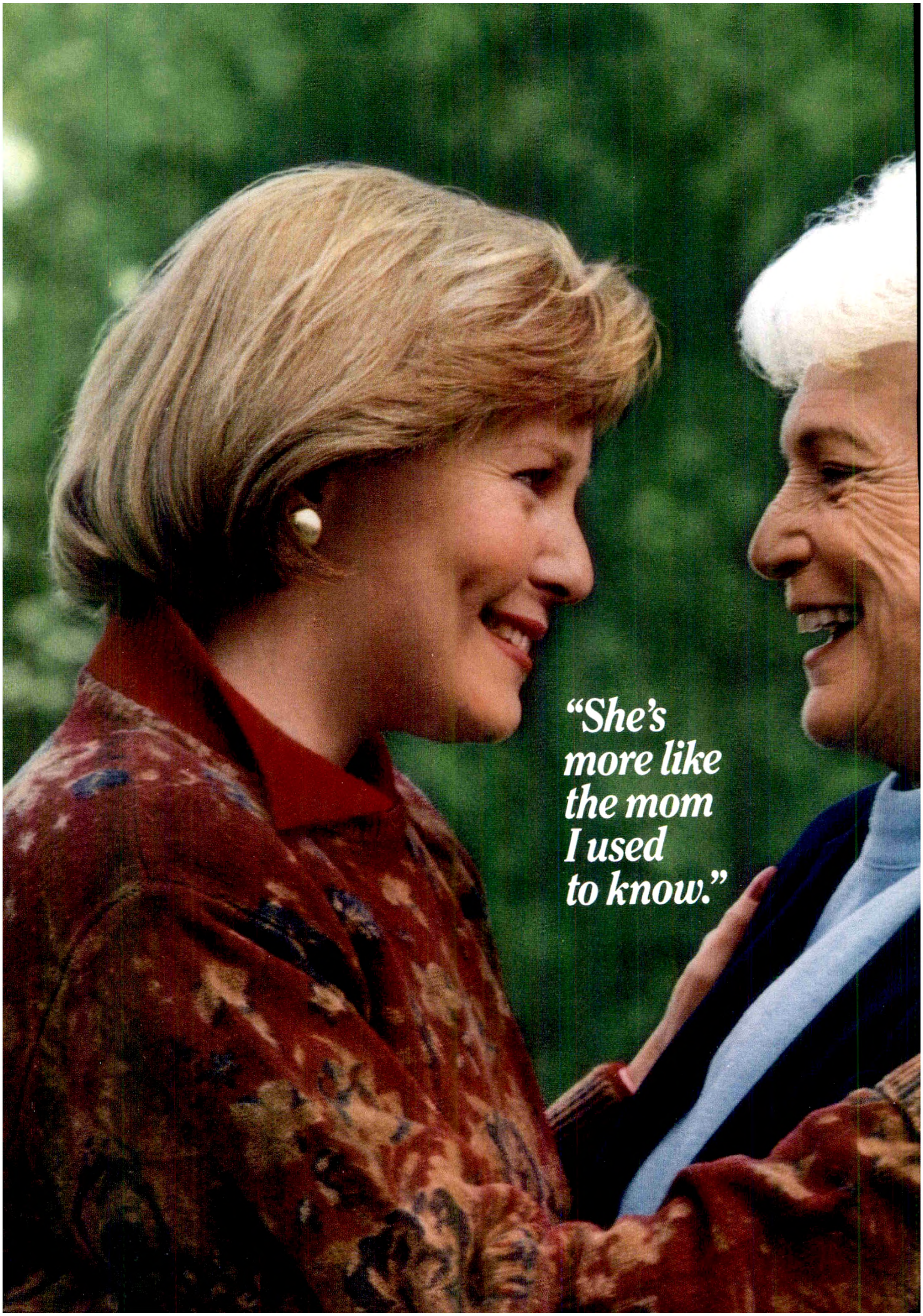
"She's
more like
the mom
I used
to know."

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When treating psychotic disorders in the elderly

Low-Dose PROLIXIN® (fluphenazine hydrochloride) provides control with a favorable side-effect profile

The disturbing psychotic symptoms seen in the elderly patient with dementia may include agitation, delusions, hallucinations, and hyperactivity.[1] Low-dose PROLIXIN frequently controls these symptoms.

A dose of 1.0 mg once a day provides effective maintenance for many geriatric patients.

Low-dose PROLIXIN has a lower incidence of those side effects commonly associated with high-dose, low-potency neuroleptics—anticholinergic effects, sedation, orthostatic hypotension, and ECG changes.*[2-4]

Low-dose PROLIXIN...available in tablets, elixir, and oral concentrate...offering precise dosing for geriatric use.

LOW-DOSE
PROLIXIN®
(fluphenazine hydrochloride)

Effective symptomatic control...
favorable side-effect profile

*NOTE: There is an increased risk of extrapyramidal effects with all high-potency neuroleptics.

Please see brief summary on last page of this advertisement.

Low-Dose PROLIXIN® (fluphenazine hydrochloride)

"She's more like the mom I used to know."

PROLIXIN® Tablets
(fluphenazine hydrochloride tablets USP)
1.0, 2.5, 5.0, and 10.0 mg—bottles of 100 and 500, and Unimatic® unit-dose packs of 100

PROLIXIN® Oral Concentrate
(fluphenazine hydrochloride oral solution USP)
5 mg/mL in bottles of 120 mL with calibrated dropper

PROLIXIN® Elixir
(fluphenazine hydrochloride elixir USP)
0.5 mg/mL—orange-flavored—in bottles of 473 mL (1 pint) and 60 mL dropper-assembly bottles

PROLIXIN®
Fluphenazine Hydrochloride
INJECTION/TABLETS/ELIXIR/ORAL CONCENTRATE

DESCRIPTION: PROLIXIN Injection (Fluphenazine Hydrochloride Injection USP), **FOR INTRAMUSCULAR USE ONLY,** provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) contains 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. PROLIXIN 2.5, 5, and 10 mg tablets contain FD&C Yellow No.5 (tartrazine). PROLIXIN Elixir (Fluphenazine Hydrochloride Elixir USP) contains 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. PROLIXIN Oral Concentrate (Fluphenazine Hydrochloride Oral Solution USP) contains 5 mg fluphenazine hydrochloride per mL, with 14% alcohol by volume.

CONTRAINDICATIONS: In the presence of established or suspected subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine hydrochloride; cross-sensitivity to phenothiazine derivatives may occur.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop, after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative, effective, less harmful treatments are *not* available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)
This potentially fatal symptom complex has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnostic evaluation is complicated; it is important to identify both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

Management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. Carefully consider the potential reintroduction of drug therapy in patients requiring antipsychotic drug treatment after recovery from NMS since recurrences have been reported. Such patients should be monitored.

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine hydrochloride cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn. Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine.

ADVERSE REACTIONS: *Central Nervous System:* Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue pro-

References:

1. Raskind MA, Risse SC: Antipsychotic drugs and the elderly. J Clin Psychiatry 47 (suppl to no. 5): 17-22, 1986.
2. Steinhart MJ: Pharmacological considerations in the use of high-potency neuroleptics in elderly patients. Geriatr Med Today 3(2): 65-73, 1984.
3. Salzman C: Treatment of the elderly agitated patient. J Clin Psychiatry 48 (suppl to no. 5): 19-22, 1987.
4. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 221, 222.

438-504

Please see brief summary continuing on adjacent page.

Continued from preceding page.

trusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

Other CNS Effects: Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occur, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage as manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed sudden flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates, and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines.

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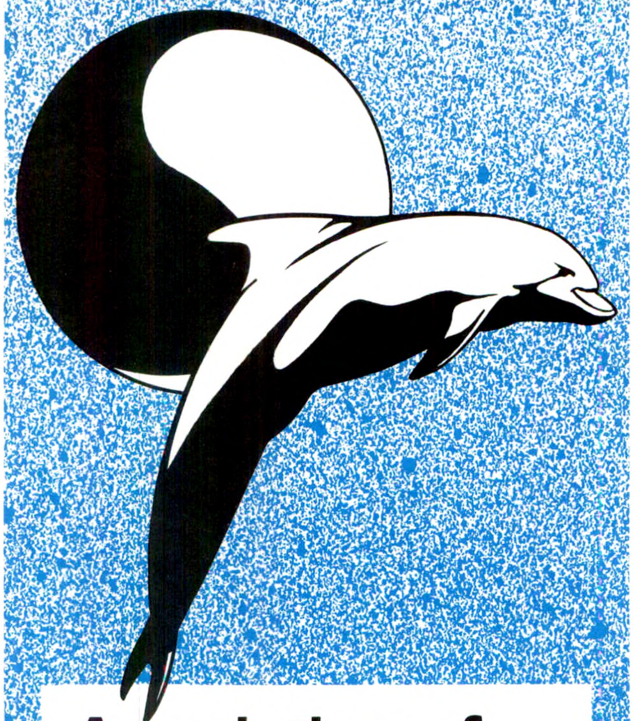

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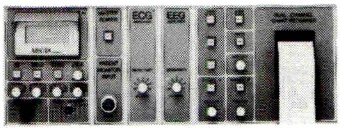

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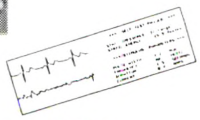

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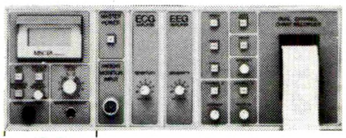

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

MAY

May 1–4, semiannual meeting, World Psychiatric Association, Sydney, Australia. Contact Fini M. Schulsinger, Secretary General, Kommunehospitalet, DK-1399 Copenhagen K, Denmark; 45-1-938500, ext. 3390.

May 2–6, annual meeting, American Pediatric Society, Washington, D.C. Contact Audrey Brown, M.D., Secretary-Treasurer, 450 Clarkson Ave., Brooklyn, NY 11203; 718-270-1692.

May 2–6, IV International Congress on Rehabilitation in Psychiatry, Orebro, Sweden. Contact S. Rost, M.D., Psychiatric Rehabilitation Dept., Regional Hospital, 700 04 Orebro 4, Sweden; 019-15-31-01.

May 4–6, annual meeting, Canadian College of Neuropsychopharmacology, Montreal. Contact Dr. P. Boska, Douglas Hospital Research Centre, 6875 LaSalle Blvd., Verdun, Quebec, Canada H4H 1R3; 514-761-6131.

May 4–7, annual meeting, American Association for the History of Medicine, Inc., New Orleans. Contact Edward C. Atwater, M.D., Secretary-Treasurer, 601 Elmwood Ave., Rochester, NY 14642; 716-275-2903.

May 4–7, annual meeting, Royal Australian and New Zealand College of Psychiatrists, Sydney, Australia. Contact Peter H. Carter, Registrar, 101 Rathdowne St., Carlton, Victoria, Australia 3053; 03-6635466.

May 4–8, annual meeting, American Psychoanalytic Association, Montreal. Contact Helen Fischer, Administrative Director, 309 East 49th St., New York, NY 10017; 212-752-0450.

May 5–8, annual meeting, American Academy of Psychoanalysis, Montreal. Contact Vivian Mendelsohn, Executive Director, 30 East 40th St., Suite 608, New York, NY 10016; 212-675-4105.

May 5–8, annual meeting, American Society of Group Psychotherapy and Psychodrama, San Diego. Contact Stephen F. Wilson, A.C.S.W., Executive Director, 116 East 27th St., New York, NY 10016; 212-725-0046.

May 7, annual meeting, American College of Psychoanalysts, Montreal. Contact Alex H. Kaplan, M.D., Secretary General, 4524 Forest Park Ave., St. Louis, MO 63108; 314-367-6243.

May 7, annual meeting, American Society of Psychoanalytic Physicians, Montreal. Contact Mrs. Deborah C. Skolnik, Executive Secretary, 904 Dryden St., Silver Spring, MD 20901; 301-681-7385.

May 7–8, annual meeting, American Academy of Psychiatrists in Alcoholism and Addictions, Montreal. Contact Sheldon I. Miller, M.D., President, P.O. Box 376, Greenbelt, MD 20770; 301-220-0951.

May 7–8, annual meeting, Association for Clinical Psychosocial Research, Montreal. Contact Stuart Hauser, M.D., Director, 74 Fenwood Rd., Boston, MA 02115; 617-232-2690.

May 7–12, annual meeting, American Psychiatric Association, Montreal. Contact Cathy Earnest, APA, 1400 K St., N.W., Washington, DC 20005; 202-682-6237.

May 7–13, annual meeting, Christian Medical Society, Psychiatry Section, Montreal. Contact Don Gent, M.D., President, P.O. Box 830689, Richardson, TX 75083-0689; 214-783-8384.

May 11–15, annual congress, Canadian Association for Medical Anthropology, Saskatoon, Saskatchewan, Canada. Contact Dr. Alexander M. Ervin, CAMA/ACAM-CESCE Conference, Dept. of Anthropology & Archaeology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0; 1-306-966-4176.

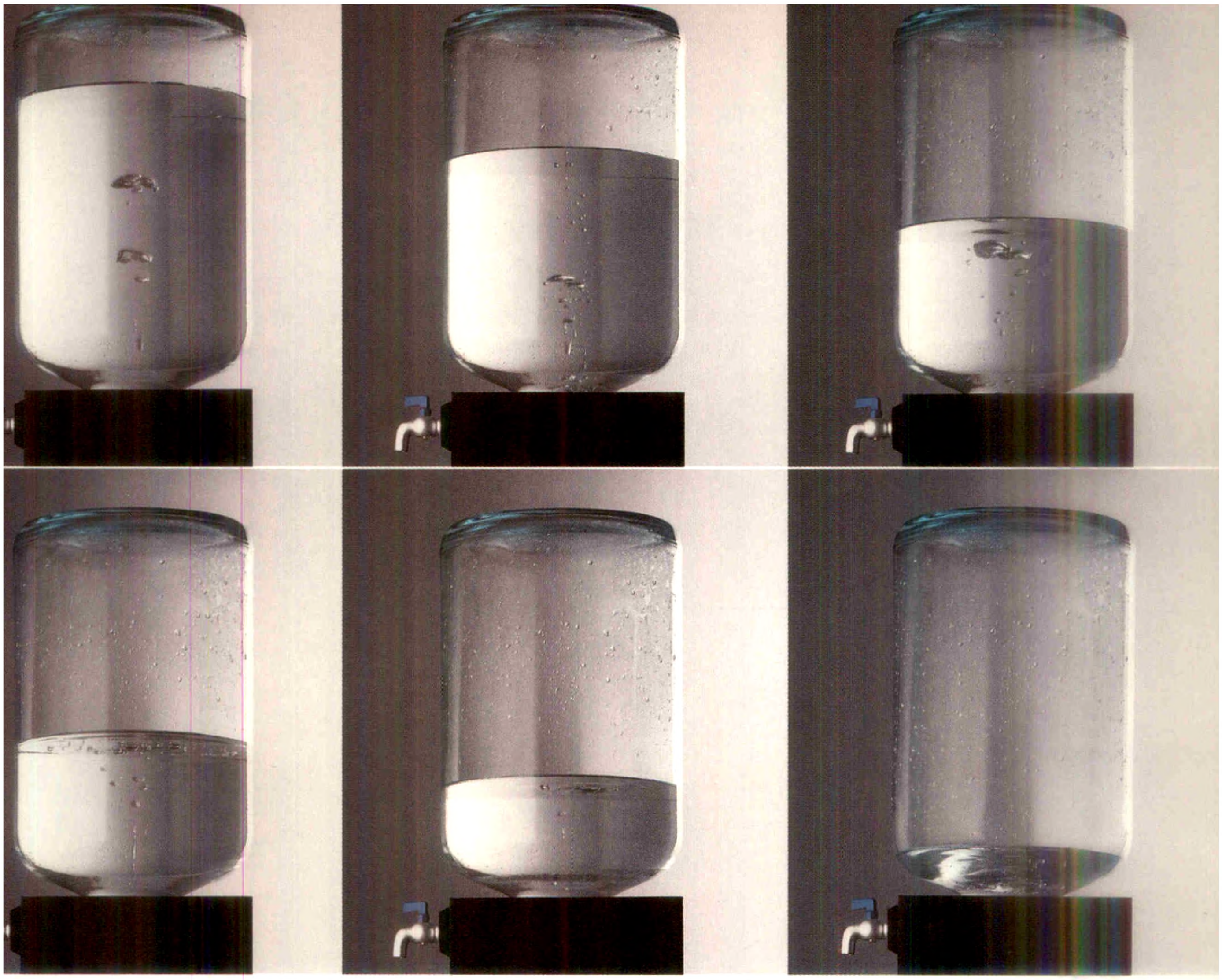
May 12, annual meeting, American Association of Psychiatric Administrators, Chicago. Contact Dave M. Davis, M.D., President, 1938 Peachtree Rd., N.W., Atlanta, GA 30309; 404-355-2914.

May 19–22, annual meeting, American Geriatric Association, Anaheim, Calif. Contact Linda Hiddenmen Barondess, Executive Vice President, 770 Lexington Ave., Suite 400, New York, NY 10021; 212-308-1414.

May 19–22, 25th Annual Meeting of the Federation of Western Societies of Neurological Science: Symposium on Pain and Epilepsy, Seattle. Contact Marjorie Schneider, P.O. Box 2586, La Jolla, CA 92038; 619-453-0572.

May 21, annual meeting, Recovery, Incorporated (The Association of Nervous and Former Mental Patients), Chicago. Contact Mary Jane Maggio, President, 802 North Dearborn St., Chicago, IL 60610; 312-337-5661.

(Continued on page A45)



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References: 1. Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. **2.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **3.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. **4.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. **5.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **6.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. **7.** Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

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Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, pare
thesias of extremities; incoordination, ataxia, tremors; periphe
neuropathy; extrapyramidal symptoms; seizures, alteration in E
patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, asso
ated sublingual adenitis; blurred vision, disturbance of accommod
tion, mydriasis; constipation, paralytic ileus; urinary retentio
delayed micturition, dilation of the urinary tract. *Allergic*—Skin ra
petechiae, urticaria, itching, photosensitization (avoid excessi
exposure to sunlight); edema (general or of face and tongue), dr
fever, cross-sensitivity with other tricyclic drugs. *Hematologic*
Bone-marrow depression, including agranulocytosis; eosinophil
purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vom
ing, anorexia, epigastric distress, diarrhea, peculiar taste, stomatit
abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in t
male, breast enlargement and galactorrhea in the female; increased
decreased libido, impotence; testicular swelling; elevation or depre
sion of blood sugar levels; syndrome of inappropriate ADH (ar
diuretic hormone) secretion. *Other*—Jaundice (simulati
obstructive), altered liver function; weight gain or loss; perspiratic
flushing; urinary frequency, nocturia; drowsiness, dizziness, wea
ness, fatigue; headache; parotid swelling; alopecia. *Withdra*
Symptoms—Though these are not indicative of addiction, ab
cessation of treatment after prolonged therapy may produce naus
headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restles
ness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperacti
reflexes, tachycardia, ECG evidence of impaired conduction, shoc
congestive heart failure, stupor, coma, and CNS stimulation with co
vulsions followed by respiratory depression. Deaths have occurr
with drugs of this class. No specific antidote is known; general su
portive measures are indicated, with gastric lavage. [PAM-Z13—7/15/

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Books Received

Eating Disorders: The Facts, 2nd ed., by Suzanne Abraham and Derek Llewellyn-Jones. New York, Oxford University Press, 1987, 159 pp., $17.95.

Brain Systems, Disorders, and Psychotropic Drugs, by Heather Ashton. New York, Oxford University Press, 1987, 523 pp., $85.00.

Suicide: Clinical and Epidemiological Studies, by Brian Barraclough with Jennifer Hughes. London, Croom Helm, and New York, Methuen, 1987, 185 pp., no price listed.

Steps to an Ecology of Mind: Collected Essays in Anthropology, Psychiatry, Evolution, and Epistemology, by Gregory Bateson. Northvale, N.J., Jason Aronson, 1987, 525 pp., $27.50.

Social Skills Training Treatment for Depression, by Robert E. Becker, Richard G. Heimberg, and Alan S. Bellack. New York, Pergamon Press, 1987, 101 pp., $21.50; $11.95 (paper).

Handbook of Intensive Brief and Emergency Psychotherapy (B.E.P.) (1983), by Leopold Bellak, M.D., and Helen Siegel, M.A. Larchmont, N.Y., C.P.S., 1987, 166 pp., no price listed (paper).

Manual for Intensive Brief and Emergency Psychotherapy (B.E.P.), by Leopold Bellak, M.D. Larchmont, N.Y., C.P.S., 1987, 52 pp., no price listed (paper).

Family Therapy: Complementary Frameworks of Theory and Practice, edited by Arnon Bentovim, Gill Gorell Barnes, and Alan Cooklin. London, Academic Press, 1987, 379 pp., $39.95 (paper).

Development Psychiatry: Mental Health and Primary Health Care in Botswana, by David I. Ben-Tovim. London, Tavistock and New York, Methuen, 1987, 226 pp., $65.00.

The Psychology of Separation and Loss: Perspectives on Development, Life Transitions, and Clinical Practice, edited by Jonathan Bloom-Fesbach, Sally Bloom-Fesbach, and associates. San Francisco, Jossey-Bass, 1987, 559 pp., $37.95.

Delivering Mental Healthcare: A Guide for HMOs, by John T. Boaz, M.D. Chicago, Pluribus Press, 1988, 184 pp., $22.95.

Current Issues in Rational-Emotive Therapy, by Windy Dryden. London, Croom Helm, and New York, Methuen, 1987, 213 pp., $39.95.

Personality and Spiritual Freedom, by Robert and Carol Ann Faucett. New York, Image Books (Doubleday & Co.), 1987, 148 pp., $6.95 (paper).

Pharmacotherapy and Mental Retardation, by Kenneth D. Gadow, Ph.D., and Alan D. Poling, Ph.D. Boston, College-Hill (Little, Brown and Co.), 1988, 343 pp., $24.50 (paper).

Feelings: Our Vital Signs (1979), by Willard Gaylin, M.D. New York, Perennial Library (Harper & Row), 1987, 242 pp., $6.95 (paper).

The Premenstrual Syndromes, edited by Leslie Hartley Gise, M.D. New York, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1988, 149 pp., $39.99.

Before Freud: Neurasthenia and the American Medical Community, 1870-1910, by F.G. Gosling. Urbana, University of Illinois Press, 1987, 185 pp., $22.95.

The Helping Group: Therapeutic Principles and Issues (1985), by Martin Lakin. Reading, Mass., Addison-Wesley Publishing Co. (Elmsford, N.Y., Pergamon, distributor), 1987, 275 pp., $19.50.

False Prophets: Studies on Authoritarianism. Communication in Society, vol. 3, by Leo Lowenthal. New Brunswick, N.J., Transaction Books, 1987, 313 pp., $24.95.

Aging: The Universal Human Experience. Selected Papers From the Symposia of the XIIIth Congress of the International Association of Gerontology, edited by George L. Maddox, Ph.D., and E.W. Busse, M.D. New York, Springer Publishing Co., 1987, 652 pp., $75.00.

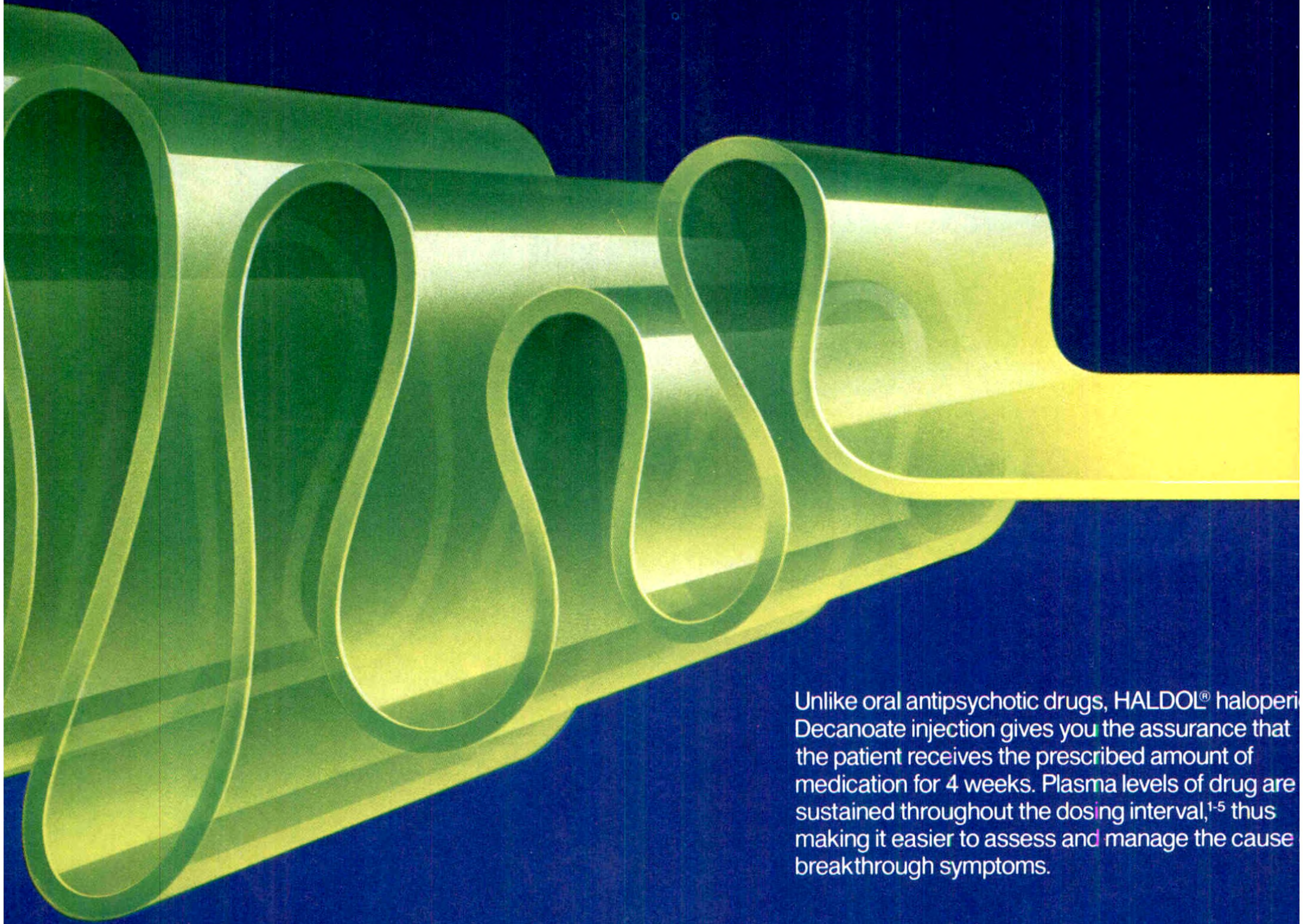
Ethopharmacology of Agonistic Behaviour in Animals and Humans, edited by B. Olivier, J. Mos, and P.F. Brain. Dordrecht, The Netherlands, Martinus Nijhoff (Kluwer Academic Publishers Group, distributor), 1987, 266 pp., $76.00.

Turning a Blind Eye? Medical Accountability and the Prevention of Torture in South Africa, by Mary Rayner. Washington, D.C., Committee on Scientific Freedom and Responsibility, American Association for the Advancement of Science, August 1987, 96 pp., no price listed (paper).

The Kundalini Experience: Psychosis or Transcendence?, by Lee Sannella, M.D. Lower Lake, Calif., Integral Publishing, 1987, 165 pp., $18.95; $9.95 (paper).

Six Steps in the Treatment of Borderline Personality Organization, by Vamik D. Volkan, M.D. Northvale, N.J., Jason Aronson, 1987, 228 pp., $25.00.

Practical Jung: Nuts and Bolts of Jungian Psychotherapy, by Harry A. Wilmer, M.D., Ph.D. Wilmette, Ill., Chiron Publications, 1987, 275 pp., $27.95.



Unlike oral antipsychotic drugs, HALDOL® haloperi
Decanoate injection gives you the assurance that
the patient receives the prescribed amount of
medication for 4 weeks. Plasma levels of drug are
sustained throughout the dosing interval,[1-5] thus
making it easier to assess and manage the cause
breakthrough symptoms.

ustained drug levels with
a single monthly dose

HALDOL® DECANOATE
HALOPERIDOL) INJECTION

ne therapeutic constant in schizophrenia

harmacokinetic profile acilitates monthly dosing

nooth, steady drug delivery has been shown to
hieve efficacy equal to oral HALDOL, but at lower
onthly doses.[1] The plasma concentrations of
loperidol gradually rise, reaching a peak at about
days after the injection, and falling thereafter, with
apparent half-life of about 3 weeks.[6]

The side effects of HALDOL Decanoate are
ose of HALDOL. The prolonged action of
LDOL Decanoate should be considered in the
anagement of side effects. During dose adjustment
episodes of exacerbation of psychotic symptoms,
LDOL Decanoate therapy can be supplemented
th short-acting forms of HALDOL. It is
commended that patients being considered for
LDOL Decanoate therapy have, at some time, been
eated with, and have tolerated well, short-acting
LDOL in order to exclude the possibility of
expected adverse sensitivity to haloperidol.
LDOL Decanoate is administered only by deep
ramuscular injection.

Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

References

1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: Efficacy, safety, and dosage equivalence. *J Clin Psychopharmacol* 1986;6(No. 1, Suppl.):30S-37S.
2. Reyntjens AJM, Heykants JJP, Woestenborghs RJH, et al: Pharmacokinetics of haloperidol decanoate. *Int Pharmacopsychiatry* 1982;17:238-246.
3. Deberdt R, Elens P, Berghmans W, et al: Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. An open multicenter study. *Acta Psychiatr Scand* 1980;62:356-363.
4. Kissling W, Möller HJ, Walter K, et al: Double-blind comparison of haloperidol decanoate and fluphenazine decanoate. Effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. *Pharmacopsychiatry* 1985;18:240-245.
5. Roose K: Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. *Acta Psychiatr Belg* 1982;82:216-223.
6. Nayak RK, Doose DR, Nair NPV. The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients (Submitted for publication).

Please see brief summary of prescribing information on next page.

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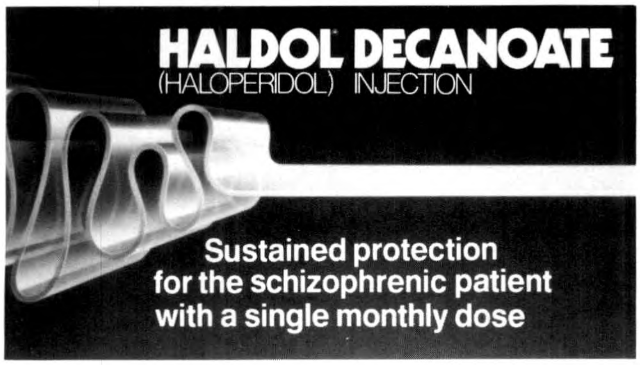

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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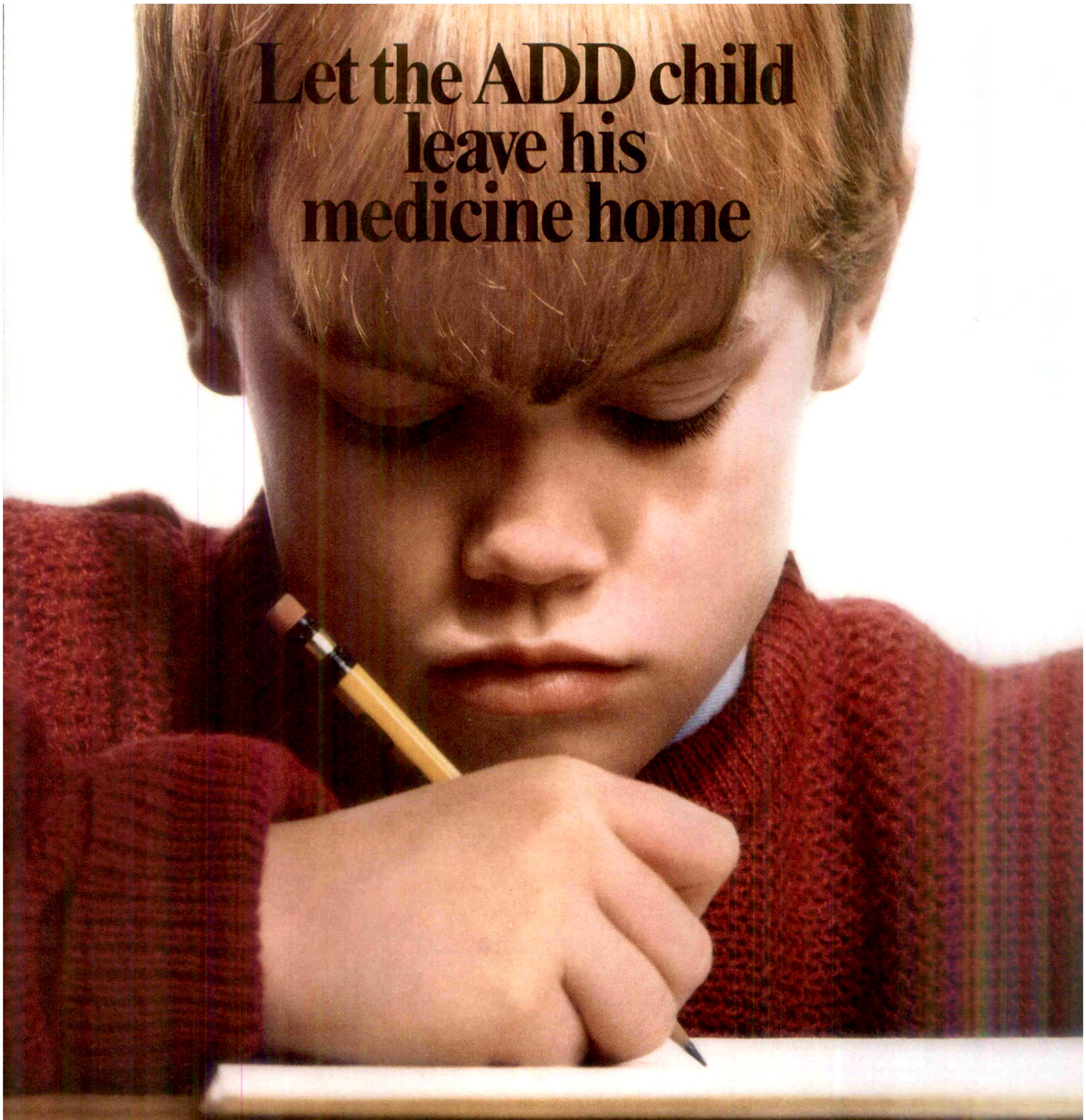

Let the ADD child leave his medicine home

Avoid the problems associated with noon dosing. One 20-mg Ritalin-SR^{C} tablet taken at breakfast provides a therapeutic effect equivalent to a standard 10-mg tablet taken twice a day.[1]

Also available: Regular tablets of 5 mg, 10 mg and 20 mg.

Greater convenience

No medicating at school

Teacher and school nurse not involved

Before prescribing, please consult Brief Summary of Prescribing Information on following page.

Ritalin is indicated as adjunctive therapy to other remedial measures (psychological, educational, social) for ADD children. Drug treatment is not indicated for all children with ADD. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis.

Once-a-day

RITALIN-SR®$^{C_{II}}$

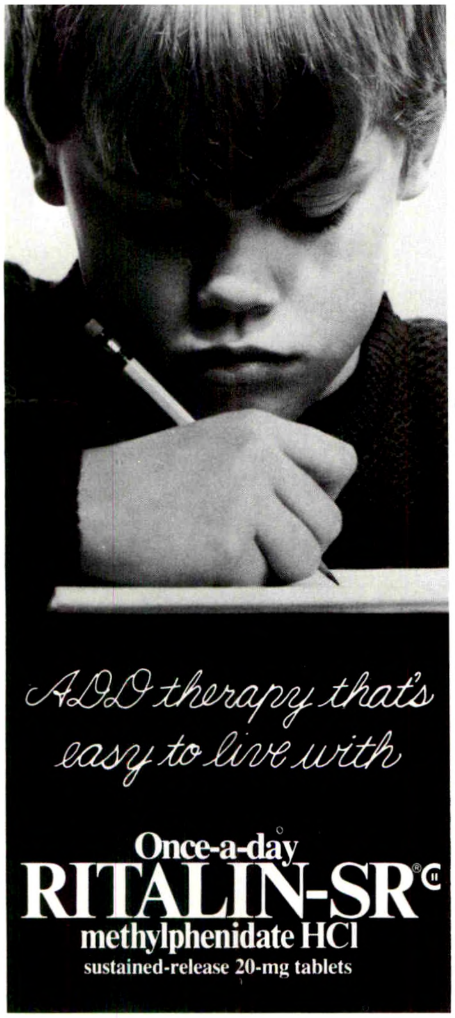
methylphenidate HCl

sustained-release 20-mg tablets

ADD therapy that's easy to live with

174-3185-A

CIBA



Ritalin® hydrochloride methylphenidate hydrochloride tablets USP

Ritalin-SR® methylphenidate hydrochloride USP sustained-release tablets

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Ritalin overdosage has not been established.

HOW SUPPLIED

Tablets 5 mg — round, yellow
(imprinted CIBA 7)

Bottles of 100	NDC 0083-0007-3
Bottles of 500	NDC 0083-0007-3
Bottles of 1000	NDC 0083-0007-4

Tablets 10 mg — round, pale green, scored
(imprinted CIBA 3)

Bottles of 100	NDC 0083-0003-3
Bottles of 500	NDC 0083-0003-3
Bottles of 1000	NDC 0083-0003-4
Accu-Pak® Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0083-0003-3

Tablets 20 mg — round, pale yellow, scored
(imprinted CIBA 34)

Bottles of 100	NDC 0083-0034-3
Bottles of 1000	NDC 0083-0034-4

Protect from light.
Dispense in tight, light-resistant container (USP).

SR Tablets 20 mg — round, white, coated
(imprinted CIBA 16)

Bottles of 100	NDC 0083-0016-3

Note: SR Tablets are color-additive free.

Do not store above 86°F (30°C). Protect from moisture.
Dispense in tight, light-resistant container (USP).

C85-55 (Rev. 11/85

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

1. Whitehouse D, et al: Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *J Clin Psychiatry* 1980;41:282-285.

CIBA

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Physicians prescribe Ativan for what it doesn't do– as well as for what it does

1

Ativan® doesn't
ignificantly delay clearance
ecause of age or kidney or
liver dysfunction

2

Ativan® doesn't
have any reported interactions
with numerous commonly
prescribed medications
(All benzodiazepines produce
additive sedative effects when
taken with alcohol or other
CNS depressants.)

3

Ativan® doesn't
have a complex
metabolism–has short duration
of action

4

Ativan® doesn't
have prolonged
accumulation–seldom
produces unwanted sedation
(Sedation, reported in 15.9%
of patients in clinical trials, was
generally mild and transitory.)

5

tivan® doesn't
use significant changes in
tal signs in cardiovascular
patients*

...it does effectively relieve anxiety

Ativan®
(lorazepam) Ⓒ IV

odiazepines have not been shown to be of benefit
ating the cardiovascular component.

7, Wyeth-Ayerst Laboratories

See important information on preceding page.

Physicians prescribe Ativan for what it doesn't do—as well as for what it does

Only Ativan offers all these benefits...

rapid relief of anxiety

---

clearance not significantly delayed by age, liver or kidney dysfunction

---

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

---

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

---

no significant changes in vital signs in cardiovascular patients*

---

short duration of action, simple metabolism

---

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

Ativan®
(lorazepam) Ⓘⓥ

Specify Ativan—and assure your patients' therapy

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Dispense as written
- Medically necessary
- Brand necessary
- May not substitute
- No substitution
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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LABORATO
Philadelphia, PA

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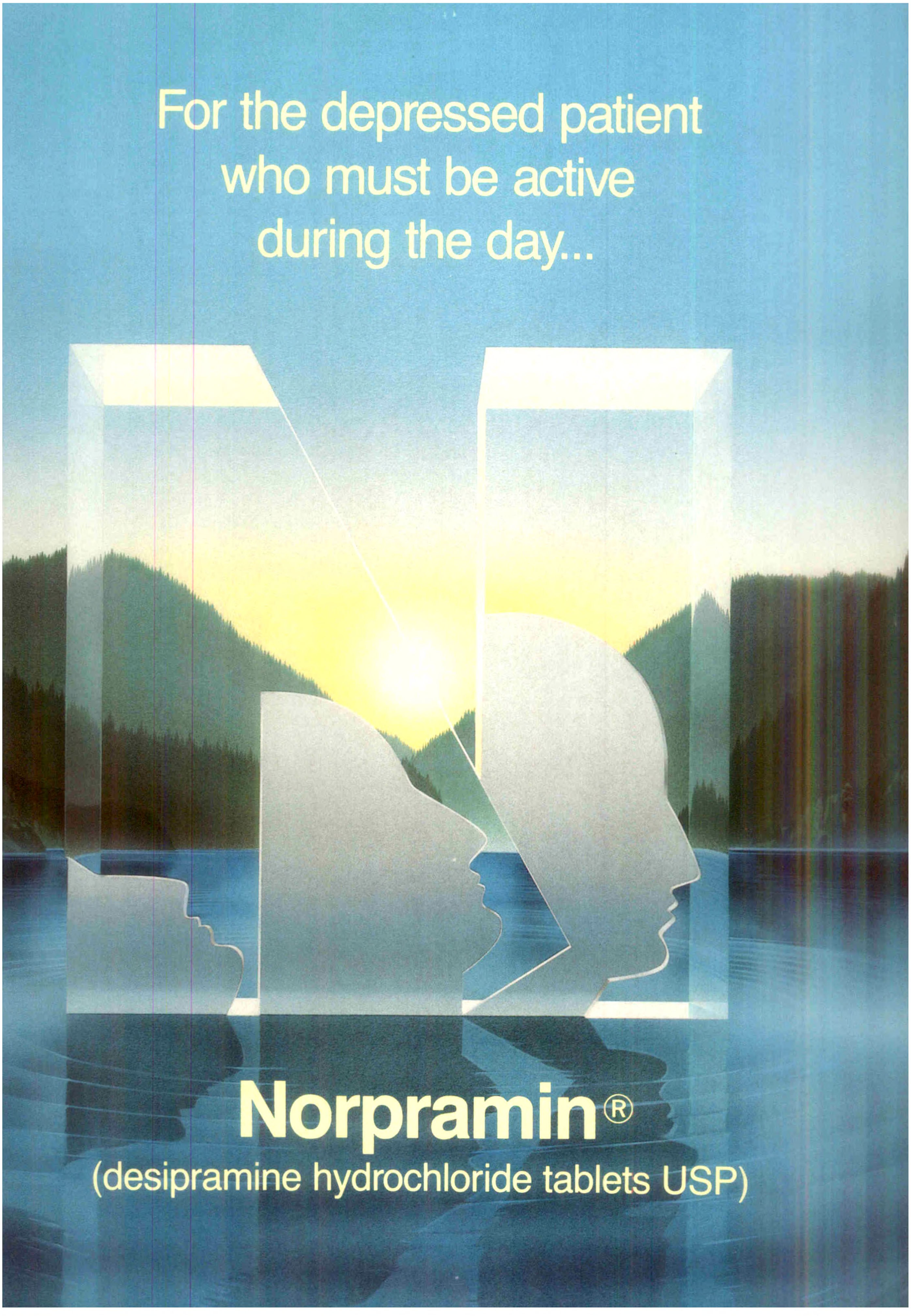

For the depressed patient
who must be active
during the day...

Norpramin®
(desipramine hydrochloride tablets USP)

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

---

a logical choice among antidepressants

Now after 23 years

- Norpramin is the #1 prescribed antidepressant by psychiatrists for the 2nd year in succession (based on a national prescription audit through July, 1987)

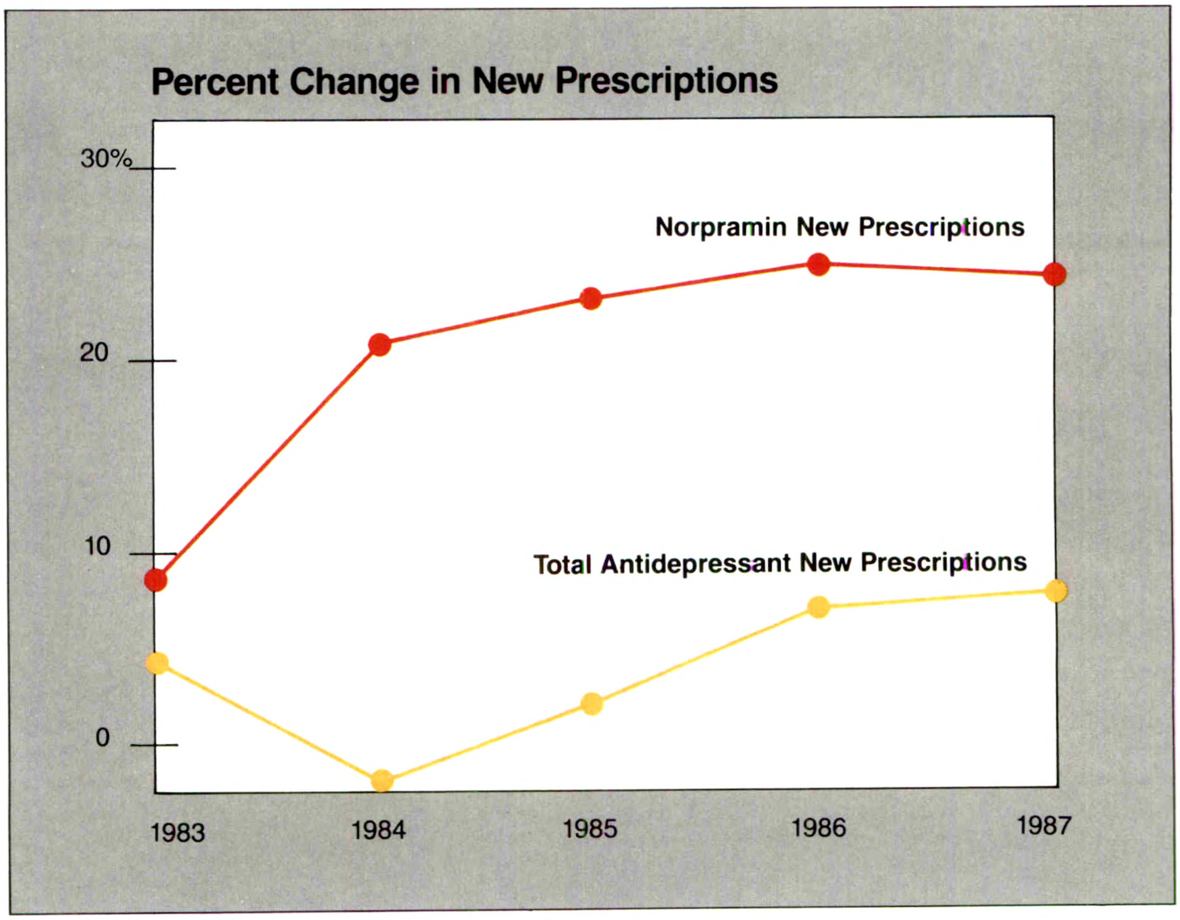

Figure 1. The red line tracks the percent change in new Norpramin prescriptions. The yellow line represents the total new prescription activity for the antidepressant market (based on data from a national prescription audit through July 1987).

Merrell Dow

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

---

a logical choice among antidepressants

The reasons are clear

- A 23-year record of efficacy in relieving symptoms of depression, including somatic anxiety,[1] sleep disturbances[2]
- Less anticholinergic activity than amitriptyline or doxepin, as shown in studies in the laboratory[3] and in normal human subjects[4,5] (see Warnings)
- Usually no excessive daytime drowsiness* (see Warnings)
- A well-defined clinical profile
- Unexcelled dosage flexibility, for patient convenience and compliance, for cost savings to patient...

*Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

References:

1. Nelson JC, Mazure C, Quinlan DM, and Jatlow PI: Drug responsive symptoms in melancholia. Arch Gen Psychiat 1984; 41:663-668.
2. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45215.
3. Snyder SH and Yamamura HI: Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiat 1977; 34:236-239.
4. Blackwell B, Stefopoulos A, Enders P, Kuzma R and Adolphe A: Anticholinergic activity of the tricyclic antidepressants. Am J Psychiat 1978; 135:722-724.
5. Petersen GR, Blackwell B, Hostetter RM, Kuzma R and Adolphe A: Anticholinergic activity of the tricyclic antidepressants despiramine [isic] and doxepin in nondepressed volunteers. Communic Psychopharmacol 1978; 2:145-150.

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See Prescribing Information on the next page

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

Convenient choice of 6 tablet strengths and once daily or divided dosage allows titration to individual response

10 mg

25 mg

50 mg

75 mg

100 mg

150 mg

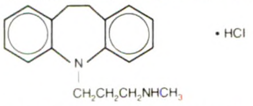
Norpramin®

(desipramine hydrochloride tablets USP)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Norpramin (desipramine hydrochloride USP) is an antidepressant drug of the tricyclic type, and is chemically: 5*H*-Dibenz [*b*,*f*] azepine-5-propanamine, 10, 11-dihydro-*N*-methyl-, monohydrochloride



INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: ACAcia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, *Metabolism*). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response. Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of th QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closel correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, an postural hypotension, should also alert the physician to the need for reduction in dosage. Plasm desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response t a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 15 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic valu characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotensio shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have bee reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaire conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts early evacuation of the ingested material and subsequent support of respiration (airway and movement circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardia pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are wel known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitaliza tion and close observation are generally advisable, even when the amount ingested is thought to be smal or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalitie should have continuous cardiac monitoring for at least 72 hours and be closely observed until well afte cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of th anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeate at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be give Because of the short duration of action of physostigmine, the effective dose should be repeated at 3 minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibili of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dos *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dialyze Because of indications that the drug is secreted in gastric juice, constant gastric lavage has be suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopress agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for t control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoi which has less central depressant effect but also has an effect on heart rhythm that has not yet been ful defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and outp are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluid Digitalization should be carried out early in view of the fact that a positive inotropic effect can achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exa opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
  NDC 0068-0007-01: bottles of 100
25 mg yellow coated tablets imprinted **MERRELL** 11 or **NORPRAMIN** 25
  NDC 0068-0011-01: bottles of 100
  NDC 0068-0011-61: unit dose dispenser of 100
  NDC 0068-0011-10: bottles of 1000
50 mg green coated tablets imprinted **MERRELL** 15 or **NORPRAMIN** 50
  NDC 0068-0015-01: bottles of 100
  NDC 0068-0015-61: unit dose dispenser of 100
  NDC 0068-0015-10: bottles of 1000
75 mg orange coated tablets imprinted **MERRELL** 19 or **NORPRAMIN** 75
  NDC 0068-0019-01: bottles of 100
100 mg peach coated tablets imprinted **MERRELL** 20 or **NORPRAMIN** 100
  NDC 0068-0020-01: bottles of 100
150 mg white coated tablets imprinted **MERRELL** 21 or **NORPRAMIN** 150
  NDC 0068-0021-50: bottles of 50

Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect fr excessive heat.

Product Information as of April, 1987 Y29

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

8-0110(NR047) MDA037

November, 1987

Printed in U.S.A

The American Psychiatric Association

1400 K Street, N.W., Washington, D.C. 20005

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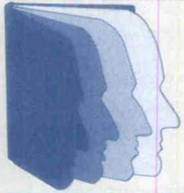

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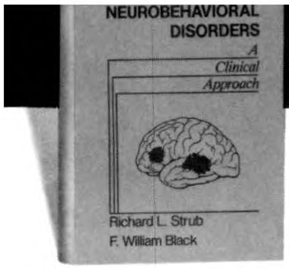

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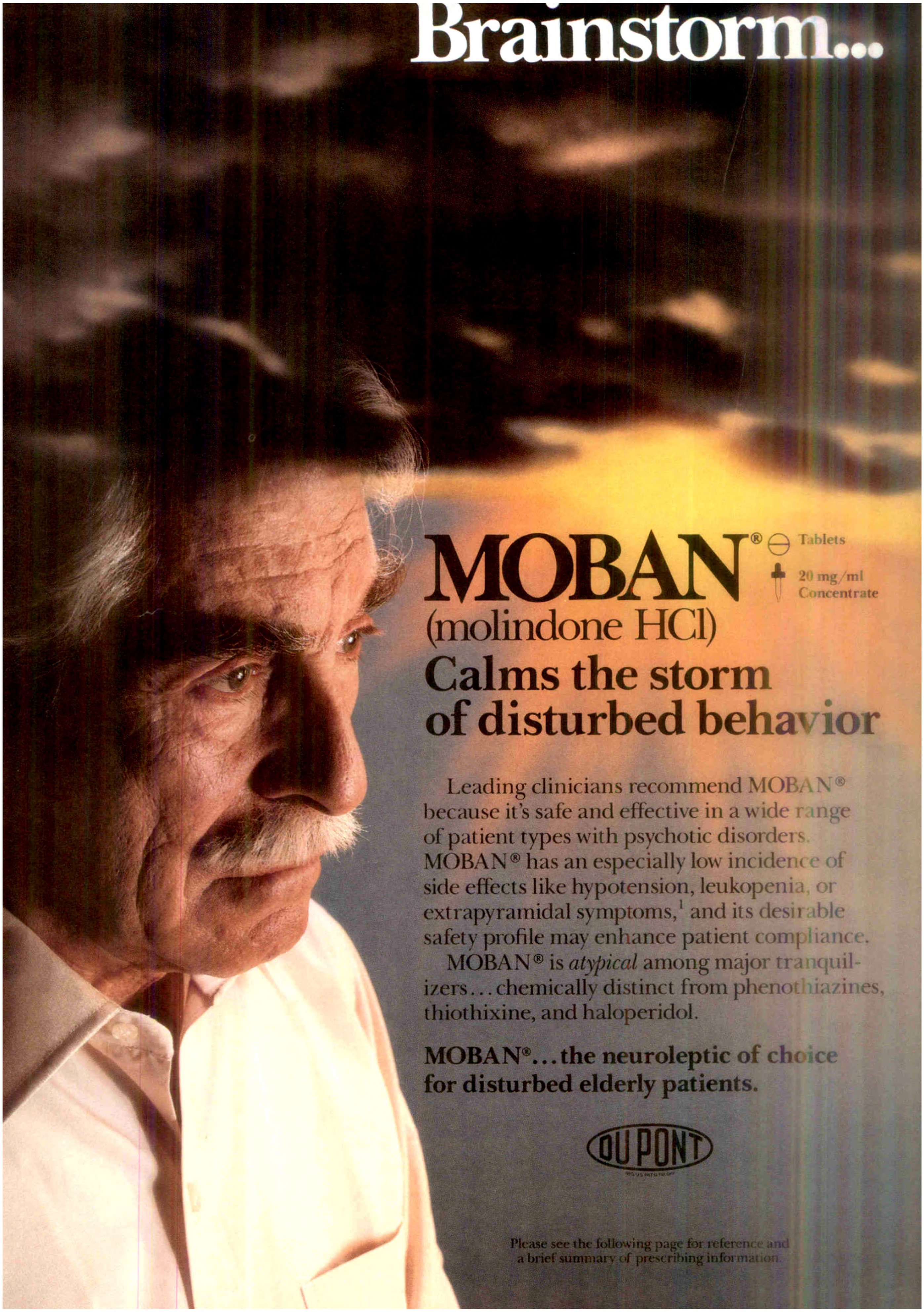

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CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause, and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women, it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may suppress or partially suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic suppression upon long-term course of the syndrome is unknown Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

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PRECAUTIONS: Some patients may note drowsiness initially, advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs, in humans convulsive seizures have been reported in a few instances This tablet preparation contains calcium sulfate as an excipient, calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis, the available evidence is considered too limited to be conclusive at this time

ADVERSE REACTIONS: CNS Effects: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals, usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms. One patient being treated with MOBAN experienced priapism which required surgical intervention, apparently resulting in residual impairment of erectile function.

Laboratory Tests: Rare reports of leucopenia and leucocytosis, treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information

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Reference: 1 Peper M Clinical experience with molindone hydrochloride in geriatric patients *J Clin Psychiatry* 1985 46 (sec 2) 26 29

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For Brief Summary, please see following page.

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BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. **2.** Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **3.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

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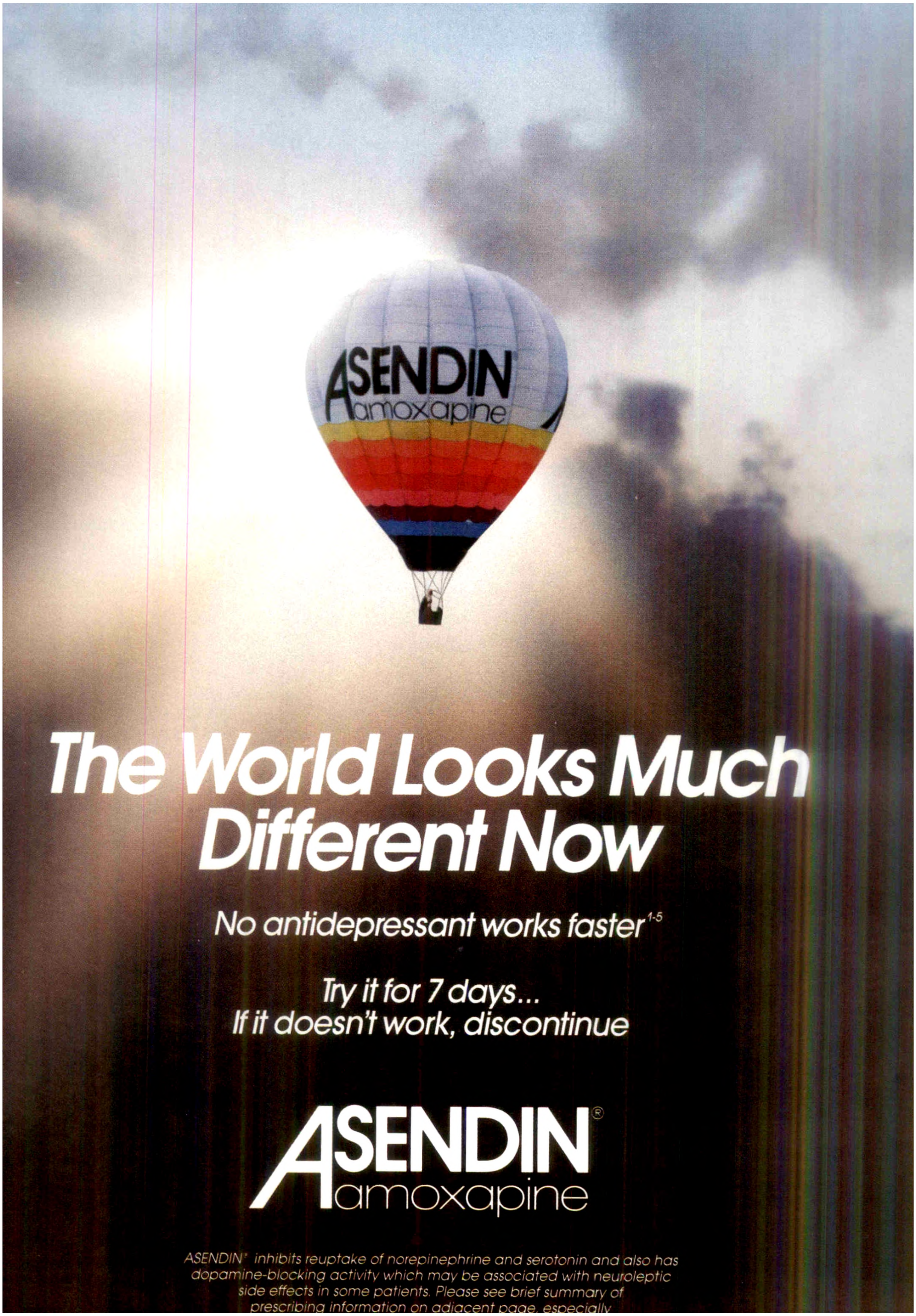
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BRIEF SUMMARY
ASENDIN® amoxapine Tablets, 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive Dyskinesia: *Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.*

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: *Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN®* amoxapine *should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.* Information for the patient: *It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired.* Drug interactions: *See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.* Therapeutic interactions: *Concurrent administration with electroshock may increase hazards associated with such therapy.* Carcinogenesis, impairment of fertility: *In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.* Pregnancy. Pregnancy Category C. *Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* Nursing mothers: *ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.* Pediatric use: *Safety and effectiveness in children below the age of 16 have not been established.*

ADVERSE REACTIONS: *Reported in Controlled Studies:* Incidence greater than 1%—*Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).*

Less frequently reported reactions were: CNS and Neuromuscular—*anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.* Allergic—*edema, skin rash.* Endocrine—*elevation of prolactin levels.* Gastrointestinal—*nausea.* Other—*dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.* Incidence less than 1%—Anticholinergic—*disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.* Cardiovascular—*hypotension, hypertension, syncope, tachycardia.* Allergic—*drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis.* CNS and Neuromuscular—*tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported.* Hematologic—*leukopenia, agranulocytosis.* Gastrointestinal—*epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.* Endocrine—*increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.* Other—*lacrimation, weight gain or loss, altered liver function.* Drug Relationship Unknown: *Reported rarely, but under circumstances where drug relationship was unknown:* Anticholinergic—*paralytic ileus.* Cardiovascular—*atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.* CNS and Neuromuscular—*hallucinations.* Hematologic—*thrombocytopenia, eosinophilia, purpura, petechiae.* Gastrointestinal—*parotid swelling.* Endocrine—*change in blood glucose levels.* Other—*pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.*

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—*sublingual adenitis, dilation of the urinary tract.* CNS and Neuromuscular—*delusions.* Gastrointestinal—*stomatitis, black tongue.* Endocrine—*gynecomastia.*

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine *overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.*

Treatment

*Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med *1982, 306: 1337-1340).*

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev 12/85

REFERENCES: 1. Hekimian LJ, Friedhoff AJ, Deever E. A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. *J Clin Psychiatry* 1978;39:633-637. **2.** Data on file, Lederle Laboratories, Pearl River, NY. **3.** Hekimian LJ, Weise CC, Friedhoff AJ. Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety/depression." *J Clin Psychiatry* 1983;44:248-252. **4.** Paprocki J, Bustamante LS, Barcala Peixoto MP, et al. A double-blind comparison of amoxapine and imipramine in depression. *A Folha Medica* 1977;74:199-210. **5.** Fabre LF. The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. *J Clin Psychiatry* 1985;46:521-524.

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Calendar

(Continued from page A20)

May 22–26, Sixteenth Annual Physician Assistant Conference, Los Angeles. Contact AAPA Director of Meetings, 1117 North 19th St., Suite 300, Arlington, VA 22209; 703-525-4200.

May 24–26, Fourth Sigmund Freud Conference, Israel Psychoanalytic Society and The Hebrew University of Jerusalem, Jerusalem. Contact Rafael Moses, Director, The Hebrew University of Jerusalem, Sigmund Freud Center for Study and Research in Psychoanalysis, Dept. of Psychology, Mount Scopus, Jerusalem 91905, Israel; 02-883380; Telex 26458

May 25–28, annual meeting, American College Health Association, Denver. Contact Stephen D. Blom, Executive Director, 15879 Crabbs Branch Way, Rockville, MD 20855; 301-963-1100.

May 29–June 1, Second European Symposium on Suicidal Behaviour, Edinburgh. Contact Stephen Platt, MRC Unit for Epidemiological Studies in Psychiatry, University Dept. of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh, EH10 5HG, Scotland, United Kingdom; 031-447-2011, ext. 4684.

May 29–June 2, annual meeting, American Association on Mental Deficiency, Washington, D.C. Contact Albert J. Berkowitz, Ed.D., Executive Director, 1719 Kalorama Rd., N.W., Washington, DC 20009; 202-387-1968.

May 30–June 3, national conference, Canadian Association of Occupational Therapists, Kitchener-Waterloo, Ontario. Contact Thelma Cameron, c/o Kitchener-Waterloo Hospital, Kitchener, Ontario, Canada N2G 1G3; 519-749-4255.

JUNE

June 2–6, Eighth International Physicians for the Prevention of Nuclear War World Congress, Montreal. Contact IPPNW, 225 Longwood Ave., Boston, MA 02115; 617-738-9404; Telex 4430017 IPPNW.

June 5–9, 9th International Symposium on Parkinson's Disease, Jerusalem. Contact Secretariat, P.O.B. 50006, Tel-Aviv 61500, Israel; 03-65471; Telex 341171 KENS IL.

June 7–10, 38th International Trade Exhibition for Medical and Hospital Equipment and Supplies INTERFAB 88, Nürnberg, West Germany. Contact NMA Nürnberger Messe- und Ausstellungsgesellschaft mbH, Messezentrum, D-8500 Nürnberg 50, West Germany; 0911-0606-0; Telex 623613 nma d.

June 9–12, annual meeting, American Association of Neuropathologists, Charleston, S.C. Contact James M. Powers, M.D., Executive Director, 171 Ashley Ave., Charleston, SC 29452; 803-792-3581.

June 11–15, annual meeting, American Nurses' Association, Louisville. Contact Dorothy Chamberlin, 2420 Pershing Rd., Kansas City, MO 64108; 816-474-5720.

June 12–14, part II examinations, American Board of Psychiatry and Neurology, Kansas City, Kan. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

June 12–15, annual conference, Association for the Care of Children's Health, Cleveland. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, ACCH, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-244-1801.

June 15–17, annual conference, Children's Aid Society of Halifax, Halifax, Nova Scotia, Canada. Contact CASH, 5244 South St., Halifax, Nova Scotia, Canada B3J 1A4; 902-425-5420.

June 18–21, annual meeting, National Congress of Parents and Teachers, Salt Lake City. Contact Robert N. Woerner, Executive Administrator, 700 North Rush St., Chicago, IL 60611; 312-787-0977.

June 23–24, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Denver. Contact Fred Sierles, M.D., Program Chair, Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064

June 26–30, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn St., Chicago, IL 60610; 312-645-5000.

June 26–July 1, annual meeting, Committee on Problems of Drug Dependence, Inc., Cape Cod, Mass. Contact Martin W. Adler, Ph.D., Executive Secretary, 3420 North Broad St., Philadelphia, PA 19140; 215-221-3298.

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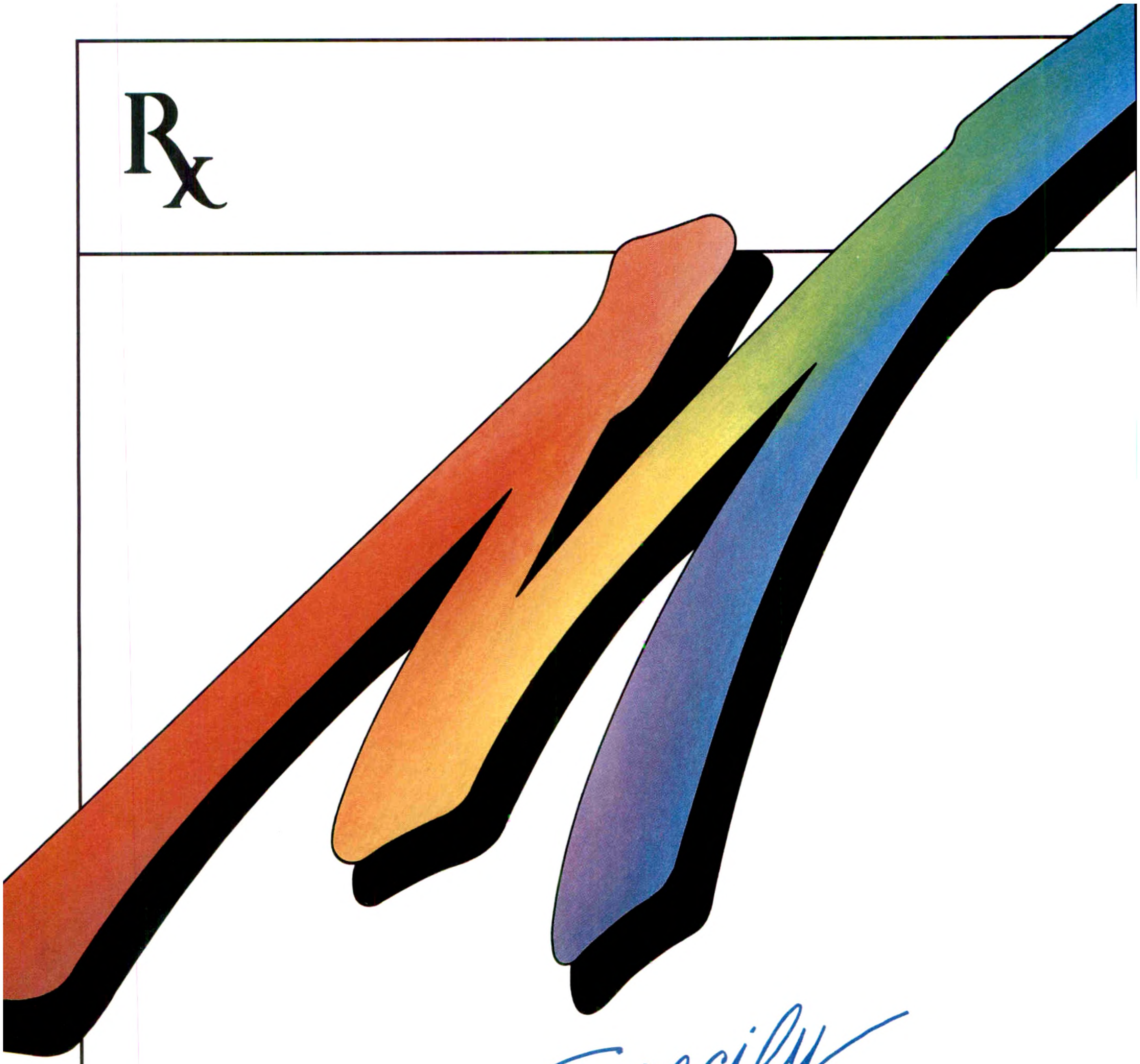

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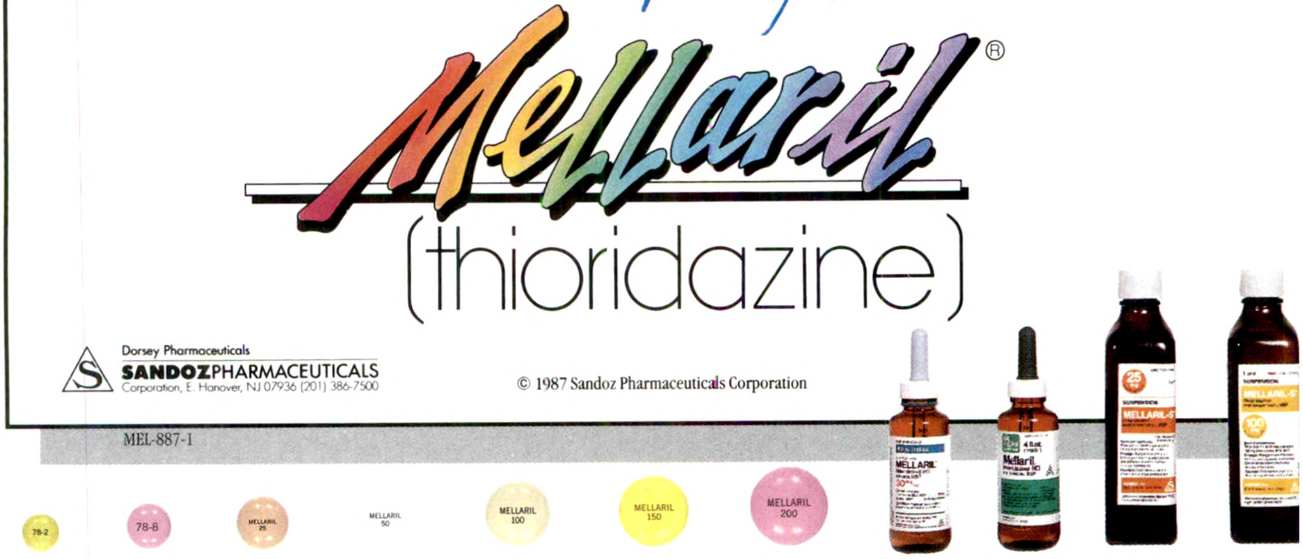

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THE AMERICAN JOURNAL OF PSYCHIATRY

Toward Rational Pharmacotherapy for Posttraumatic Stress Disorder: An Interim Report

Matthew J. Friedman, M.D., Ph.D.

There is growing evidence that medication can alleviate symptoms associated with posttraumatic stress disorder (PTSD). Recent research also suggests that PTSD has a unique biological profile consisting of alterations in sympathetic arousal, the neuroendocrine system, and the sleep/dream cycle. This profile distinguishes PTSD from both major depression and panic disorder. Medication appears to alleviate PTSD symptoms associated with sympathetic hyperarousal and intrusive recollections of the trauma but seems ineffective against avoidant symptoms. Pharmacotherapy alone is rarely sufficient to provide complete remission of PTSD. Symptom relief provided by medication facilitates the patient's participation in individual, behavioral, or group psychotherapy.

(Am J Psychiatry 1988; 145:281–285)

Of approximately 1,000 articles cited in the 1986 edition of Arnold's bibliography on combat-related posttraumatic stress disorder (PTSD) (1), less than 20 address pharmacotherapy for PTSD. Instead, most of the current literature has focused on the history, epidemiology, symptomatology, diagnosis, and nonpharmacological psychotherapeutic treatment of PTSD. There may be three reasons for this apparent lack of interest in pharmacotherapy for PTSD. First of all, PTSD appears to be the quintessential psychological disorder in which exposure to a stimulus (catastrophic stress) is followed by a conditioned emotional response and negatively reinforced avoidance behavior. Probably no other disorder in *DSM-III* can be conceptualized by classic learning theory (i.e., two-factor theory [2]) as well as PTSD can. Second, there has been strong resistance in some psychiatric circles to acknowledging the validity of PTSD as a diagnostic entity. In fact, pockets of such resistance even exist at some facilities within the Veterans Administration, despite the large number of psychiatric patients with combat-related PTSD. Third, there has been little time since the publication of *DSM-III* for systematic evaluation of either the biological correlates or the clinical psychopharmacology of PTSD.

Among clinicians who do accept the validity of this diagnosis, PTSD has rekindled old therapeutic controversies. Questions about the efficacy of amobarbital-induced narcosynthesis have received new interest after decades of neglect in the published literature (3). There are proponents of long-term hospitalization who argue that effective treatment for severe PTSD requires at least 3 months of intensive inpatient psychotherapy and that standard 2–3-week hospitalizations can achieve little more than symptom reduction or crisis intervention (4). Another controversy concerns the proper role of pharmacotherapy in the treatment of PTSD.

Many proponents of intensive psychotherapy for PTSD complain that medication is counterproductive. While conceding that relief of some PTSD symptoms can be achieved through pharmacotherapy, they argue that not only does such superficial improvement fail to affect the core disease but also such symptomatic improvement may so distract patients from the major therapeutic agenda that they terminate treatment prematurely. This is an old controversy—as old as the introduction of the first psychotropic agents into psychiatric practice—and it fails to acknowledge research showing that psychotherapy and pharmacotherapy are usually complementary treatments (5). On the other hand, there is sufficient evidence to support the idea

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that drugs may be an inadequate treatment for this disorder (6).

This review should be considered an interim report on rational pharmacotherapy for PTSD. Rational pharmacotherapy is possible either when the pharmacological action of an effective drug will reverse the biological alterations associated with a specific disorder or when double-blind trials have demonstrated the efficacy of a given drug for a given disorder. With regard to biological correlates of PTSD, a few studies have appeared which suggest that people who meet the *DSM-III* criteria for PTSD may also have a unique pathophysiological profile which is distinct from that of panic disorder or affective illness. With regard to the clinical psychopharmacology of PTSD, to my knowledge no double-blind trials have been published to date (although a number are currently in progress), but there is a small body of open trials and case reports that can be reviewed at this time.

BIOLOGICAL CORRELATES OF PTSD

It is reasonable to suggest that any disorder which can persist for decades (7) is associated with measurable biological alterations, but there is little research on this question. The few biological investigations of PTSD that have been conducted can be categorized as studies of alterations in sympathetic arousal, the neuroendocrine system, and the sleep/dream cycle.

Psychophysiological research has indicated that patients with PTSD exhibit higher levels of sympathetic nervous system activity and reactivity. Earlier findings in uncontrolled studies by Dobbs and Wilson (8) on EEG alpha rhythm, heart rate, and respiration rate and by Gillespie (9) on muscle tension were confirmed and extended by Blanchard et al. (10), who compared male Vietnam veterans with PTSD to age and sex-matched nonveteran control subjects. The PTSD patients showed higher baseline heart rates, systolic blood pressure, and forehead electromyogram (EMG) responses. More importantly, these PTSD patients exhibited significantly greater physiological responses to an audiotape of combat sounds played at gradually increasing volume levels. The heart rate, systolic blood pressure, and EMG responses of PTSD patients were so much greater than those of control subjects that blind raters correctly classified them 95.5% of the time. Similar results have been obtained in other laboratories (11, 12).

Mason et al. (13, 14) showed that PTSD patients had a significantly higher urinary norepinephrine/cortisol ratio than patients with bipolar disorder, major depressive disorder, paranoid schizophrenia, and undifferentiated schizophrenia. The authors suggested that higher urinary norepinephrine levels are consistent with psychophysiological findings which show increased sympathetic nervous system activity and reactivity (10–12). Lower urinary cortisol levels are consistent with earlier findings which suggested that denial and psychological defenses can exert a strong suppressive effect on urinary corticosteroid levels (15–21).

Research on sleep and dreaming also suggests that there may be a unique biological pattern associated with PTSD. Veterans with combat-related PTSD exhibit sleep abnormalities such as increased REM latency, less REM sleep, diminished stage 4 sleep, and reduced sleep efficiency (22–25). Kramer believes that PTSD is essentially an arousal disorder. He and Kinney showed that patients with PTSD are much more physiologically reactive than control subjects to nonspecific auditory stimuli during sleep (26). In addition to an abnormal sleep pattern, disturbed dreaming is a prominent abnormality in chronic PTSD (27, 28). Friedman (29) noted that traumatic nightmares associated with PTSD do not fit into either of Kramer's nightmare categories (27): they do not meet criteria for REM-related dream anxiety attacks nor are they typical of a stage 4 night terror/nightmare syndrome. Furthermore, van der Kolk and associates (28) showed that traumatic nightmares may arise out of various stages of sleep and are not confined to REM sleep alone.

To summarize, all biological research to date is consistent with the hypothesis that chronic PTSD is a hyperarousal state associated with excessive sympathetic nervous activity. Van der Kolk et al. (30), extrapolating from the animal model of inescapable shock, hypothesized that the hyperarousal, traumatic nightmares, and flashbacks that characterize PTSD are related to long-term potentiation of locus ceruleus pathways to the hippocampus and amygdala. They also suggested that such hyperreactivity is further enhanced by fluctuations in endogenous opioid levels in response to reexposure to traumatic situations.

Kindling is another neurobiological model with potential applicability to PTSD. Post and Kopanda (31) suggested that endogenous catecholamines might kindle limbic nuclei in the same way as cocaine, thereby producing endogenous schizophrenic or manic-depressive psychosis. Similarly, the chronic sympathetic hyperarousal observed in PTSD patients might also kindle limbic nuclei, thereby producing a relatively stable neurobiological alteration. Such a hypothesis would explain why untreated PTSD can persist for decades (7). It suggests that carbamazepine might be an effective treatment for PTSD. It also suggests that benzodiazepines and other γ-aminobutyric acid agonists or synergists should be particularly efficacious for treatment of PTSD, since benzodiazepine receptor binding is increased substantially during the development of limbic kindling (32–34).

CLINICAL PSYCHOPHARMACOLOGY

The current literature on the pharmacotherapy of PTSD consists entirely of reports of open trials and case reports. A number of double-blind trials are in progress, but none have been reported. It seems that any pharmacological agent which can dampen the hyperarousal associated with PTSD should have a palliative if not curative role in treatment. Therefore, it is not surprising that the drugs which have been reported to be effective are clonidine, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), propranolol, lithium, and benzodiazepines (29, 35–37). Kolb et al. (38) conducted successful trials of clonidine and propranolol in patients with chronic combat-related PTSD. Lithium (37, 39) has also been found effective in treating chronic PTSD.

There are several reports on the efficacy of the MAOI phenelzine (40–43). MAOIs are attractive agents to consider because they are antipanic agents, antidepressants, and powerful inhibitors of REM sleep. Phenelzine may not be the best alternative for combat veterans with PTSD because of the high rate of alcoholism and chemical abuse/dependency observed in this population (44). Therefore, it may have wider applicability for survivors of sexual trauma or natural disasters, for whom rates of alcoholism are probably much lower.

Tricyclic antidepressants have been used the most in treating PTSD. Although no reports of controlled trials have been published, several reports attest to the effectiveness of these agents (29, 45–47). Tricyclics (especially imipramine) dampen hyperarousal through their antipanic action, reduce intrusive recollections, suppress flashbacks, and reduce traumatic nightmares. In addition, the antidepressant action of tricyclics is of great value, since so many patients with chronic PTSD also meet the *DSM-III* criteria for major depression. The tricyclics are less risky than MAOIs to prescribe for patients with alcohol or substance abuse/dependency problems. Finally, since tricyclics enhance endogenous opioids through potentiation of synergistic serotoninergic mechanisms (48), their effectiveness in PTSD may also be attributed to their modulation of the sharp fluctuations in endogenous opioids postulated by van der Kolk and associates (30) in their inescapable-shock model of PTSD.

Benzodiazepines are effective (37) and may have unique applicability if kindling has a role in the pathophysiology of PTSD. Obviously, they should be prescribed with caution for patients with alcoholism, chemical dependency, or a previous history of drug addiction (29). Currently, there is considerable interest in the unique triazolobenzodiazepine alprazolam because of its demonstrated antipanic and antidepressant properties (49, 50). However, there is growing concern about addiction and withdrawal problems with this drug (51, 52).

Antipsychotic agents have no place in the routine treatment of PTSD. Even paranoid-type symptoms and the unique hallucinatory experiences known as flashbacks are usually treated effectively by reducing the level of arousal with tricyclic antidepressants or other agents that I have mentioned. Neuroleptics are, of course, the drugs of choice for frank psychosis, but it is quite unusual in chronic PTSD. Indications for prescribing neuroleptics for patients with PTSD include aggressive psychotic symptoms (frequently paranoid), overwhelming anger, self-destructive behavior, and frequent flashback episodes characterized by visual and auditory hallucinations of traumatic events (29, 36).

It is important to note that pharmacotherapy alone is rarely sufficient to provide complete remission of PTSD. Symptom relief provided by medication enables the patient to participate more thoroughly in individual, behavioral, or group psychotherapy.

DIAGNOSTIC CONSIDERATIONS

Most drugs that are effective for PTSD are also useful both in major depression and in panic disorder. This is true not only for tricyclics and MAOIs but also for alprazolam. In addition, major depression and panic disorder share many of the same symptoms as PTSD. Therefore, it is useful to review current knowledge about the biology and clinical psychopharmacology of each of these disorders in order to clarify their distinguishing features as well as their similarities.

In addition to their responsivity to tricyclics, MAOIs, and lithium, patients with PTSD and those with major depression have many symptoms in common, such as dysphoria, guilt, grief, anhedonia, irritability, social withdrawal, and insomnia. Such similarities, however, should not obscure some of the fundamental differences between these two disorders. Major depression and PTSD differ on a number of sleep characteristics. 1) There is diminished REM sleep in PTSD and excessive REM sleep in major depression. 2) REM latency is increased in PTSD and diminished in major depression. 3) Dreams and nightmares appear in REM and non-REM sleep of patients with PTSD but only in REM sleep of those with major depression. There also appear to be endocrinological differences with regard to the corticosteroid system. Major depression is often associated with an abnormal dexamethasone suppression test (DST) result, indicating hyperactivity of the hypothalamic-pituitary-adrenocortical axis (53). Although no studies of the DST in PTSD have been published to my knowledge, PTSD appears to be a hypoadrenocortical state, as indicated by lower urinary free cortisol levels (13, 14). Sympathetic arousal and anxiety appear to be hallmarks of PTSD (10–12), whereas they are both less prominent and more variable in major depression. Finally, propranolol is an effective treatment for PTSD (38) but may exacerbate depressive symptoms in individuals with a diathesis for major depression (54).

There are also similarities between PTSD and panic disorder. Both disorders are associated with sympathetic hyperarousal and sudden surges of anxiety. Both respond to tricyclic antidepressants, MAOIs, and propranolol (38, 55). Both disorders are often associated with depressive symptoms. It has been postulated that locus ceruleus dysregulation plays a major role in panic disorder (56) as well as in PTSD (30). And, finally, it has been suggested that PTSD flashbacks meet the *DSM-III* criteria for panic attacks (57). There are important differences between the disorders, however. In panic disorder, attacks are spontaneous and primarily physiological in nature, whereas PTSD attacks are triggered by a meaningful stimulus and are primarily meaningful psychological events. Stage 4 sleep is reduced in PTSD but significantly increased in panic disorder (58). A familial tendency toward the spontaneous development of panic disorder has been demonstrated (59), whereas PTSD is never spontaneous and occurs only after exposure to catastrophic stress. Marijuana can precipitate panic attacks in patients with panic disorder (60, 61, and manuscript by S.M. Fishman et al.) but appears to have a calming effect on combat veterans with PTSD. Finally, we await a systematic evaluation of sodium lactate infusion in PTSD patients to see whether it can precipitate attacks, as it can in panic disorder (62).

To summarize, PTSD, major depression, and panic disorder all appear to have unique biological profiles despite a considerable overlap in symptoms and responsivity to tricyclics and MAOIs.

MESHING TREATMENT WITH SYMPTOMS

In *DSM-III-R* the diagnostic criteria for PTSD (pp. 247–248) have been modified in a way that is more consistent with the embryonic biological characterization of this disorder. The four criteria are 1) exposure to catastrophic stress, 2) reexperiencing the trauma spontaneously or after exposure to emotionally charged stimuli through intrusive recollections, nightmares, or flashbacks, 3) persistent avoidance of emotionally charged stimuli through numbing of responsiveness, avoidance of charged stimuli, or psychogenic amnesia, and 4) persistent hyperarousal as indicated by insomnia, irritability and rage, difficulty concentrating, hypervigilance, and increased startle response. It appears that target symptoms under the second and fourth criteria (intrusive recollections and sympathetic arousal, respectively) are most responsive to pharmacotherapy. Avoidant symptoms such as alienation, detachment, and psychic numbing rarely respond to medication unless depression is also present. This is reminiscent of the observation that neuroleptics attenuate the positive but not the negative symptoms of schizophrenia.

CONCLUSIONS

It is clear that there is no definitive pharmacological treatment for PTSD. Drug treatment alone is never sufficient to alleviate the suffering in PTSD. Pharmacotherapy is primarily useful as an adjunct to psychological (intrapsychic and/or behavioral) treatment of PTSD. Drug-mediated attenuation of intrusive or hyperarousal symptoms facilitates therapeutic work on guilt, grief, intimacy, rage, moral pain, and other issues.

It also appears that catastrophic exposure to trauma is followed by stable biological alterations in the sympathetic nervous system, neuroendocrine system, and sleep/dream cycle. Such alterations appear to be unique to PTSD and distinguish it both from major depression and from panic disorder despite similarities in symptomatology. It is hoped that better understanding of the biological correlates of PTSD will lead to a rational pharmacotherapy for this disorder.

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DSM-III Axis IV Revisited

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Clinicians have traditionally inquired about stressful life events preceding the onset of a psychiatric disorder. Axis IV of DSM-III *attempted to improve on this by suggesting that a wide range of events be considered and that the information obtained be integrated into a global rating of severity. After reviewing recent evidence, the authors suggest that this process might result in ratings with lower reliability than expected. They also discuss some of the methodological difficulties in this field and explore directions for further research.*

(Am J Psychiatry 1988; 145:286–292)

Since the *DSM-III* multiaxial system has come into widespread use, clinicians have been expected to make and record a number of judgments about their patients in addition to the ones required in the traditional diagnostic classifications. At face value these changes appear to be a step forward because they acknowledge that a psychiatric diagnosis should be more than just a label and should provide a maximum of useful information for identifying and dealing with a patient's psychiatric condition (1). These innovations also recognize that the clinical picture cannot be adequately captured by assigning to the patient only one of a set of alternative diagnoses (2). However, the adoption of a multiaxial system, although well received by the psychiatric community all over the world (3–5), has meant a departure from the *International Classification of Diseases,* with consequent risks for psychiatric communication (6, 7). At present, the mental disorders section of the 10th edition of the *International Classification of Diseases* (*ICD-10*) (8) is being prepared. A revision of *DSM-III* (*DSM-III-R*) has just been published, and *DSM-IV* is not far in the future. The general adoption of a similar multiaxial system—if proven to be useful—could help APA and the World Health Organization (WHO) get back into step (3, 7).

The inclusion of separate axes for recording ratings of psychosocial factors is a departure from previous practice that has received less critical attention than some of the other novel aspects of *DSM-III* (9) Although there is agreement that psychosocial stress and premorbid functioning are particularly important variables that may have etiological or prognostic value (2), it does not necessarily follow that formal definition and incorporation as separate axes in each and every diagnosis is the best way to ensure that this information will be considered. Nor does it ensure that the data will be recorded (10, 11).

The use of the supplementary axes was made optional shortly before the adoption of *DSM-III,* and it was intended that, in time, empirical data would answer the questions about their utility (12). It is probable, however, that the role of these axes will be a more contentious issue in the future than it was before *DSM-III* because many specialty groups have already developed or suggested other axes relevant to their own needs (13, 14). Some of these may be of sufficient general importance to be added to future multiaxial systems or even to displace the present axes. In considering this, it is important to recognize that there is a tradeoff between the aim of comprehensiveness (which tends to lead to a proliferation of axes) and the aim of parsimony (which tends to restrict the number of axes to those on which there is widespread agreement) (13, 15). For these reasons, it would be desirable to have evidence about the results achieved by including the supplementary axes to guide decisions about future revisions, but the lack of empirical research on axes IV and V (13) still renders it difficult to judge the usefulness of these axes. It may be that this lack of research indicates that practitioners have found the supplementary axes interesting enough to have but not good or practical enough to use as clinical and research tools Some support for that view has been supplied by a 1985 survey of directors of residency training (11) which showed that, although residents were expected to use the first three axes of *DSM-III* in three-quarters of the programs surveyed, they were expected to use axes IV and V only in one-quarter of them. It is also of note that most of the reliability studies on *DSM-III* now quite numerous (16), either do not report on or have omitted these axes.

The introduction of the psychosocial axes was justified on the grounds that they might help in manage-

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ment planning, might have prognostic value, and might be useful in clinical research (12). Since then, criticisms, particularly of axis IV, have abounded (12). The object of this paper is to examine in the light of more recent research whether axis IV has met the expectations initially raised, to analyze its methodological shortcomings, and to explore avenues for its improvement. The historical background and some of the wider issues surrounding this axis have already been reviewed by Williams (12, 13).

RELIABILITY OF AXIS IV

It has been assumed that the reliability of axis IV, according to the results of the field trials, is "quite good" or "fair" (13, 17; *DSM-III,* p. 465). Reliability estimates in these trials ranged from 0.59 to 0.75 (mean across groups and phases=0.65) (*DSM-III,* p. 472). However, methodological problems in those studies raise some doubt about the generalizability of the results (18), as Rutter and Shaffer (2) have also noted. The basic unit in all the field trials consisted of two colleagues from the same institution—probably with similar biases—rating two successive patients (361 pairs of clinicians rated 723 patients; each pair rated a mean of two patients). Ratings of two consecutive patients tend to be comparative judgments that increase concordance of rank ordering rather than judgments referred independently to a common yardstick and do not allow for changes over time to develop (18, 19).

More recent studies also support the inference that the field trials may have led to estimates of the reliability of axis IV ratings which cannot safely be generalized to other situations (18). Mezzich et al. (20) reported an intraclass correlation coefficient (ICC) of 0.25 in a case history study in which 67 independent clinicians made multiaxial *DSM-III* diagnoses for 27 case histories, divided into nine subsamples of three case files, each judged by 6–9 raters. Elsewhere (18) we reported an intraclass correlation coefficient of 0.44 in a sample of 140 adolescents diagnosed independently by the same pair of clinicians over a period of 10 months.

The discrepancy between the field trial results and those of Mezzich et al. (20) might be explained if it is assumed that the pairs of field trial judges, each of whom had interviewed the patient, were basing their judgments on interview information which was in some way different from the kind of information which is typically recorded in the case file, as used by the judges in the study of Mezzich et al. (20). Although one study (21) supports that assumption for axis I diagnoses, it has not been shown that this can also be applied to axis IV. In our study (18), 48% of the patients had been interviewed by one of the judges while the other judge worked from the case file; in the remaining cases both judges worked from files prepared by other clinicians. If the interviewing judge had relevant information unavailable to the case file judge, agreement between these judges would be expected to be lower than agreement between two case file judges, but no such difference was found. Moreover, reliability studies of axis V using interviews with adult patients (22) and case files (18, 20) also showed less reliability than the field trials. However, further studies will be necessary to clarify this issue.

Our interpretation of these results is that when additional possibilities of variation are included by extending the basic unit of the field trials (for example, more judges diagnosing more patients [20] or the same number of judges diagnosing a long series of patients over a considerable time period, using interviews or case files [18]), agreement on axis IV ratings is low and that this range of variation is likely to represent more accurately the way in which such judgments are made and used in clinical practice (18). The implications for the research use of axis IV are also important. It is usually accepted that a research measure should have a reliability of at least 0.8 and that when individual judgments are less reliable than this the mean of several such ratings should be used. According to Shrout and Fleiss (23), it can be estimated that a minimum of five judges would be needed to yield a mean rating with a reliability of 0.8, based on the mean figure (ICC=0.44) across the three reliability studies (*DSM-III,* p. 472; 18, 20); this is clearly impractical. For those reasons we do not believe that axis IV as it stands provides an adequate measure for either clinical or research purposes.

A study which seems to belie this conclusion is that of Zimmerman et al. (24), who argued that axis IV ratings are valid because associations were found between their ratings and other clinical variables in a sample of 130 depressed patients. It would appear, however, that all the ratings were made by a judge who rated the patient after completing a semistructured interview covering 152 life events. The relationships found between the different life event variables and axis IV ratings may reflect only the rater's own biases or consistency rather than an independent association. Even though it is probable that ratings of axis IV made in this way would be reliable (25), such a finding would at most indicate the reliability of ratings of axis IV made after first using a lengthy life events schedule. This, however, is not the manner in which axis IV ratings are expected to be made; hence, the relevance of these findings to the reliability or validity of axis IV as such is questionable.

SOURCES OF UNRELIABILITY

The definition of axis IV requires the clinician making the rating to take into account the different aspects of stress and to reflect the summed influence of multiple stressors when necessary. However, the only assistance given is a list of potential stressors and a set of examples of the appropriate ratings for some individual stressors. This leaves ample scope for differences of interpretation at each stage of the rating process, and it seems likely that the poor overall reliability of axis IV ratings reflects the joint influence of all these sources of variation. In seeking to find the sources of unreliability it is useful to consider the various stages of stressor assessment separately (25).

Identification of Stressors

The first stage, that of eliciting potential stressors, can be done with near-perfect agreement if enough time and effort is devoted to it. For instance, the structured interview procedure of Brown and Harris (26) may take up to half a day. Although there can be little doubt that this method comes close to the ideal, if incorporation of such a procedure were necessary to make axis IV acceptable, then the attempt to include psychosocial stress as part of routine diagnostic evaluation might as well be abandoned without further ado. Even Paykel's semistructured interview (25), which takes 30–75 minutes, is too long for routine use (24), although it is of interest that a mean interpair agreement on "specific event occurrence" of 95% can be obtained with this technique. This figure compares favorably with the 63% mean interpair agreement on presence versus absence of events on a list of 28 stressors reported by Russell et al. (27) in their case file study of *DSM-III* reliability and with the 48% agreement found by Rutter et al. (28) on the presence versus absence of seven psychosocial "situations" in their study of a multiaxial classification of child psychiatric disorders.

DSM-III specifies no particular procedure for eliciting information about stressor occurrence, and although it provides a list of examples it would be unrealistic to suppose that this list is systematically used. The identification of stressors during an unstructured interview or an interview structured for other purposes is certain to be sporadic and idiosyncratic (25), so that the absence of any formal procedure for stressor identification seems likely to be one of the major weaknesses of axis IV.

Analysis of the stressors listed in the course of one of our studies (29) has shed some light on the problems of unstructured stressor identification. In a series of 159 patients referred to an adolescent psychiatric unit, we found that agreement on the number of stressors identified was poor (index of positive agreement=0.32) and agreement on specific event occurrence was also low (index of positive agreement=0.36) on average. However, when stressors were classified according to their relative severity (the most severe event listed for a patient versus all other events) and according to their absolute severity, two trends emerged. First, judges were much more likely to agree on the identity of the most severe stressor listed for a patient than they were for other events. This was particularly true if the stressor was absolutely as well as relatively severe. The maximum index of positive agreement was 0.85 for the most severe event listed for patients with axis IV ratings of 6 or 7. Conversely, when judges agreed on the identity of the most severe stressor, axis IV reliability was significantly higher (index of positive agreement=0.61) than when they disagreed (index of positive agreement=0.20). The index of positive agreement on "specific event occurrence" when minor stressors were considered was low in all cases (around 0.20). These results are no more than a confirmation of the commonsense view that clinicians are likely to agree about which stressors are present when there is something fairly important to identify and that they are more likely to agree on axis IV ratings if they have first agreed on what it is that they are rating.

Another way of looking at the problem is by asking if all stressors are equally important to identify. If they are not, then the limited time available may be best spent on improving identification of the more important ones. Brown et al. (30) found that 42% of a clinical sample of depressed women had experienced markedly threatening events during the previous year, in contrast with only 9% of a control group. Brugha et al. (31), in a survey of recent life events in a random sample of the general population, found that a substantial proportion of stressfulness was accounted for by a small group of severe life events (serious illness, injury or death of people who were close, and other major losses). These studies suggest that short schedules of severe events are likely to be more useful in a general clinical setting than longer inventories which include minor stressors.

Assessing Impact of Individual Stressors

There are many techniques available for assessment of the impact of individual stressors; the following review is intended only to illustrate the range of options available. Methods differ on three main points: the definition of "impact," the objectivity of the judgment, and the scale on which the judgments are recorded.

Henderson et al. (32) required ratings on seven dimensions of "impact" (emotional upset, disruption, adjustment, depression, anxiety, anger, and helplessness). Isherwood et al. (33) required ratings on five (amount of readjustment required, desirability of the event, desirability of the outcome of the event, expectedness of the event, and amount of control over the course of the event and its outcome). Paykel (25) required two (objective negative impact and independence), and Holmes and Rahe (34) required ratings on only one dimension (amount of social readjustment required). An alternative to making multidimensional ratings is to obtain a unidimensional rating but then classify the events into distinct groups, such as "threat" and "loss" (35) or "entrances" and "exits" (24, 36).

If the labels for the dimensions are compared with the aspects of stress that are to be taken into account when making an axis IV severity rating, the composite nature of the axis IV definition of severity is clear. Moreover, since judgments in these theoretically distinct dimensions tend to be highly correlated (33), *DSM-III* may not be so very wide of the mark in considering them together during the rating process itself rather than combining them afterwards (37). Thus, this aspect of the *DSM-III* procedure seems to be a reasonable and practical compromise.

Of the different procedures available to assess the impact of stressful life events, the most objective is "consensus scaling": stressors are defined in general terms and judged for impact by professionals (38) or by individuals who have recently experienced the event (32). The mean rating assigned by such a sample defines a "standard" impact score on a particular dimension, and these scale values can be combined across samples and dimensions by using a variety of statistical procedures (32). This does not entirely solve the problem of obtaining an objective measure, but at least it ensures that the same biases will be applied uniformly to any patient reporting a stressor. At the other extreme, it is possible to use the patient's own subjective judgment of impact for each identified stressor. Such judgments have been demonstrated in a prospective study to have greater predictive value than consensus scaling of the same events (37), but in the clinical context and in the more usual retrospective study (39) there is the problem of "effort after meaning" (26) or "retrospective falsification" (40). For these reasons, the procedure favored by Paykel (25) is an adaptation of the "contextual threat" judgment of Brown et al. (30): the judgment is made by the clinician, taking into account the detailed circumstances but ignoring the patient's subjective reaction. This is very similar to the *DSM-III* procedure, except that *DSM-III* provides in addition a set of examples that in practice amounts to a suggested consensus scale for some stressors. Thus, the *DSM-III* solution is again a compromise, a necessary one in the clinical situation where the patient is usually the main informant, but it is arguable whether a sympathetic clinician's ratings are more objective than those of the patient (25).

Some information on the reliability with which severity ratings can be made for individual stressors comes from a scaling study that we have reported elsewhere (41). In that study a sample of 54 professionals working with adolescents were asked to rate "severity" (defined as in *DSM-III*) of each of 77 psychosocial stressors. They used either the 7-point *DSM-III* scale (N=17), a 5-point scale obtained by collapsing the two outermost categories of the *DSM-III* scale (N=20), or a 3-point (low/medium/high) scale (N=17). No examples were given for any of the three scales. It was found that reliability calculated across the 77 items was 0.46 for the 7-point scale, 0.48 for the 5-point scale, and 0.34 for the 3-point scale. Thus, even when judges do not have to identify stressors, assess them for relevance, or ignore individual vulnerability, they still show poor agreement in rating severity using the *DSM-III* definition. In our study this did not seem to depend on the type of scale used or on the rater's reported experience.

A further complication is that different events may be perceived as having different degrees of stressfulness by individuals from diverse cultural backgrounds, as Alarcon (42) pointed out. For instance, the raters in our study (41) perceived chronic parental conflict as a more severe stressor than death of a brother or sister—in disagreement with the *DSM-III* examples—and the latter as less severe than death of a grandparent—in disagreement with Coddington (38). Rather than misjudgment, these discrepancies may simply reflect different perceptions of the relationships and roles within the family in the Australian and American cultures. If that is the case for stressors in general, this would tend to diminish the universality of *DSM-III* (4, 9, 42).

Assessing the Impact of Multiple Stressors

When the impact of multiple stressors is to be assessed, the *DSM-III* instructions leave the decision entirely to the discretion of the clinician. Hence, it is of some interest to know how often this unspecified process is likely to be required. The report of 1,111 multiaxial *DSM-III* diagnoses by Mezzich et al. (10) provided these data. The diagnoses were recorded on a standard form that allowed up to four stressors to be listed. The percentages of cases in which zero through four stressors were listed were 16%, 25%, 32% 20%, and 7%, respectively, so that it would seem that on about half of the occasions the rating required an assessment of cumulative impact of more than one stressor. Thus, the absence of any rule for performing this process of integrating information is of some practical importance.

Unfortunately, the life events literature offers a number of competing solutions. Brown et al. (26, 30) considered that once a single major event has been experienced, others do not matter a great deal. This avoids the absurdity of making mountains out of an accumulation of molehills, but at the other extreme it would suggest that a succession of major events is no more stressful than one or that an accumulation of mild stressors is not pathogenic (43). Paykel (25) noted that the usual procedure of adding up the impact scores of all reported events produces scores which correlate highly with one produced by simply counting the events. This is because major events are rare, trivial stressors tend to be forgotten or omitted, and the bulk of the total score for any individual is made up of moderately severe events carrying much the same impact weights, so that the total weighted impact score will usually be very similar to the number of events multiplied by a moderate impact score. Thus, criticism of the vagueness of the *DSM-III* requirement to reflect the summed influence of multiple stressors needs to be tempered by the observation that it relies on the clinician's common sense to solve a problem which life events researchers have so far found intractable.

We have attempted to explore this issue by asking four clinicians making independent *DSM-III* diagnoses of a series of adolescents to identify and rate each stressor separately, following the *DSM-III* instructions, and subsequently make a rating of the overall axis IV severity (29). We found that in 40 of the 108 ratings made on 27 patients, two or more stressors were identified. The overall severity rating was equal to the rating of severity of the most stressful event identified in 31 of these cases. In none of the nine cases in which the ratings were different was there more than a 1-point difference between them. This suggests that, in practice, clinicians tend to assign the same rating to the most severe event and to axis IV overall, giving little weight to the other events. Similar results have been obtained when rating severity of pre- and perinatal complications (44). However, further research in this area is needed.

Relevance of Stressors

DSM-III indicates that only stressors believed to have contributed to the onset and/or exacerbation of the current disorder should be considered. This requirement has been repeatedly criticized (2, 12) because the role that stressful life events play in the development and maintenance of psychiatric disorder is still controversial (32, 45–47). This criterion is also likely to influence reliability because it introduces another subjective element—what the clinician may consider etiologically significant—in the rating process. To our knowledge, no empirical research exists in this area so far as axis IV is concerned.

DISCUSSION

A review of axis IV may appear premature at this stage, when so little specific research is available. However, the comments that a "radical transformation" is needed (7) and that a revision is "imminent" (48), when the empirical research on which such revision should be based is lacking, makes a review necessary if only to point out the gaps which still exist in our knowledge and the need for further research.

Much of the data presented here refers to children and adolescents. It might be argued that these results do not necessarily apply to adult or elderly patients. However, in the field trials the mean reliabilities across phases for adults (ICC=0.63) and children and adolescents (ICC=0.67) were similar. As already presented in this paper, subsequent evidence indicated that the latter is likely to be an overestimate, and there is no reason to believe that reliability for adults would behave in a different way if the possibilities for variation were similarly increased, as has been shown for axis V ratings (22). It might also be argued that axis IV criteria for children and adolescents may be incorrect, but the severity examples at least seem to be reasonably accurate (41). Therefore, we cannot find evidence to support the assumption that problems in making axis IV ratings in children or adolescents are in any substantial way different from the ones likely to be encountered in adult or elderly patients.

This research, although limited, does appear to cast some doubt on the reliability of axis IV. Consequently, care should be exercised when evaluating studies that try to establish the validity, predictive power, or usefulness of this axis if reliability estimates are not reported (49–51). Lack of reliability is likely to be a major difficulty to be overcome before axis IV can make a sound contribution to the diagnostic system.

Given the subjective and idiosyncratic way in which stressful events are identified in unstructured clinical interviews (25), it appears that one of the main weaknesses of axis IV is the lack of more specific guidelines for obtaining this basic information on which all subsequent decisions must be based. Consequently, tinkering with the ratings or the aggregation process is likely to create an impression of statistical objectivity but to have no practical benefits (52).

In our opinion, revision of axis IV needs to begin at the initial stage: the guidelines for identifying stressors. There are two routes that can be followed: either to make a serious effort to adapt the time-consuming but reliable procedures of life event researchers or to abandon the attempt to cover all possible stressors. We favor the latter alternative for reasons already given. A short schedule of severe stressors such as the one suggested by Brugha et al. (31) can easily be explored during an interview. It is hardly likely that either clinician or patient would consider this a waste of time, since careful inquiry about life events preceding the onset of a psychiatric disorder is a time-honored clinical endeavor (53). The severe stressors found, if any, should then be listed. About one-third of the participants in the field trials supported this solution (17). That would be a purely descriptive approach (more in line with the stated *DSM-III* philosophy), and clinicians or researchers could interpret the resulting information as they saw fit. In particular, the distinctions between chronic and acute stressors and between different types of stressors—which are of concern to many researchers (2, 7, 12, 47)—would be less of a problem in this context, since decisions about classification and aggregation could be made independently of data collection. The listing of a stressor is also likely to convey more useful clinical information than a severity rating by itself, as Kendell (7) stated, and would help the universality of *DSM-III* because it sidesteps the criticism that severity ratings may vary depending on the country or cultural background (41, 42).

The next question is whether anything worthwhile is achieved by asking judges to rate or aggregate the severity of stressors. If all events are important, they are likely to receive similar severity ratings, so that event counts and weighted summary scores will be highly correlated (25, 33). In other words, there is not much difference in principle between counting by fives and counting by ones. Moreover, rating may actually degrade reliability; even when judges have events listed in a schedule, they assign quite disparate ratings of severity (41). In short, if a schedule of severe events is used, asking clinicians to rate them might well reduce reliability rather than increase it. Clinicians also find the task of rating severity as required by axis IV quite difficult (41, 54).

CONCLUSIONS

The inclusion of axis IV is a worthwhile attempt to ensure that clinicians consider and record psychosocial stressors in every diagnosis. However, axis IV—because it is a compromise among different views in the absence of a widely accepted and workable scheme—appears to have suffered from a confusion of aims or, as Malt (3) put it, "wants to ride two horses at the same time," seeking to be clinically meaningful and also reliable according to current standards of life events research. The difficulty of this aim did not escape the task force in drawing up *DSM-III,* and it was made clear from the start that axis IV was a diagnostic dimension to be tested and modified depending on the advance of knowledge in this area (9, 13). However, hasty changes are unlikely to be of benefit and may create confusion for the users of *DSM-III* if they are carried out before more specific answers to some of the problems described are found.

The volume of literature on psychosocial stress leaves little doubt that this is an important variable whose possible role in the etiology and course of mental disorder deserves continuing attention. Although the assessment of stressors in *DSM-III* falls short of the state of the art in the general life events literature, the assessment of disorder in much of that literature falls equally behind the state of the art in *DSM-III* (47). Thus, if axis IV could be improved, its routine use in large clinical populations has the potential to make a substantial contribution to our understanding of the relationships between stress and disorder.

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Regular Articles

Depression and Panic Attacks: The Significance of Overlap as Reflected in Follow-Up and Family Study Data

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Ninety-one patients with panic attacks limited historically to depressive episodes had more severe depressive symptoms and were less likely to recover during a 2-year follow-up than 417 depressed patients who did not have panic attacks. Family study data clearly distinguished another 15 patients with panic disorder and secondary depression; interviewed relatives of panic disorder patients were significantly less likely to have primary depression and significantly more likely to have various anxiety disorders. These data support the hierarchical system by which many of the contemporary diagnostic systems separate panic disorder and major depression.

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The frequent coexistence of anxiety and depressive symptoms has raised two broad, long-debated questions, one practical and the other more academic. The latter concerns the number of discrete diseases presumably involved in a patient. Does an individual who suffers from both depressive and anxiety symptoms have two separate illnesses? Does he or she have, instead, just one primary illness, in which symptoms suggesting the other condition are only epiphenomena? Does he or she have a third illness unrelated to panic disorder or major depressive disorder? Finally, is there, in fact, only one disease, and are panic disorder, major depressive disorder, and intermediate symptom mixtures simply different manifestations of that disease?

More practical questions apply as well. Do individuals experiencing both panic and depressive syndromes have different prognoses from those who display one or the other syndrome in purer form? Moreover, if these individuals indeed suffer from only one or the other primary illness, how might the clinician identify the correct one?

We used family study data to approach these questions and, in doing so, emphasized panic attacks, since panic disorder, among the various anxiety syndromes, has recently attracted the most attention. Thus, if the admixture of affective symptoms and panic attacks signifies a separate, or third, illness, this mixed-symptom phenomenon should breed true: the relatives of probands who have both panic attacks and major depression should be more likely to exhibit the coexisting syndromes than the relatives of probands who exhibit only depression or only panic attacks. On the other hand, a high proportion of family pedigrees containing both panic disorder and major depression (in separate individuals) would strengthen the hypothesis that the corresponding probands are manifesting a genotypical coincidence of the two disorders. If panic disorder, major depression, and the syndromal mixture are all manifestations of a single disorder, the expected familial patterns of illness will depend on how these "forms" are conceptualized. If the mixture represents the most severe and genetically penetrant or loaded form, rates of panic disorder and major depression should be highest among relatives of a proband who has the mixture. If, on the other hand, panic disorder and major depression represent extremes of a continuum, the relatives of probands at one end should

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have higher rates of both illnesses than do relatives of probands at the other end.

If the data point to the two-disease model, the remaining task is to discern one illness from the other. Two alternative conventions apply. According to one, the syndrome that predominates, either in cross-section or over time, is taken to be the primary illness (1). The other convention is embodied in the criteria of Feighner et al. (2), in the Research Diagnostic Criteria (RDC) (3), and in *DSM-III* and distinguishes these illnesses hierarchically. Thus, only panic attacks that occur independently of an affective syndrome (according to the RDC, at least 2 months before onset or 2 months after remission) are considered indicative of a panic disorder, while a cluster of depressive symptoms indicates an affective disorder whether or not panic attacks are also present. We used our data to test the value of this latter convention.

The presence of panic attacks may have prognostic importance regardless of whether they indicate a separate illness. In turn, panic attacks may only be important prognostically when they indicate a primary diagnosis of panic disorder. These practical questions call for follow-up data. The National Institute of Mental Health-Clinical Research Branch Collaborative Program on the Psychobiology of Depression:Clinical Studies has collected, within one overall protocol, data well suited to each of the issues we have mentioned. It included a family study, a detailed baseline phenomenological assessment, and a prospective follow-up that has now lasted 2 years.

METHOD

Patients with major affective disorders were invited to participate in the collaborative study shortly after admission to the hospital or within 2 months of their first outpatient appointment at any of the five participating tertiary care centers. The inclusion criteria specified that all subjects be 17 years of age or older, Caucasian, English-speaking, knowledgeable about both biological parents, and free of any brain syndrome, terminal illness, or mental deficiency (IQ less than 70).

Systematically trained raters used medical records and the full Schedule for Affective Disorders and Schizophrenia (SADS)(4) to assess baseline psychopathology and to reach an RDC diagnosis. These same raters then recontacted each patient at 6-month intervals and, using the Longitudinal Interval Follow-Up Evaluation (LIFE)(5), charted the subsequent course of symptoms and quantified their impact on psychosocial functioning.

Treatment, though at all times naturalistic, was carefully monitored through LIFE interviews and through medical record review. The week-by-week dose of each drug taken during each follow-up interval was recorded, as was the number of ECTs received, if any. The resulting data were condensed by using drug equivalencies determined by reference to the relevant literature (available from the authors on request). For example, 150 mg of imipramine was considered the equivalent of 75 mg of nortriptyline, and 300 mg of chlorpromazine was considered the equivalent of 6 mg of haloperidol.

Our analyses quantified outcome in several ways. By RDC and LIFE convention, patients were considered to have "recovered" if they had experienced for 8 or more contiguous weeks no more than one or two of the eight RDC depressive symptoms and these were present to only a mild degree. Psychosocial impairment due to psychopathology was rated on a 5-point scale in each of several areas; a score of 3 indicated at least some impairment. The scores were collapsed to yield the proportion of patients with any impairment in that area. To reflect the level of depressive psychopathology characterizing a sustained period, we averaged the depressive symptom level (expressed on a 5-point scale for each week) across the final 26-week period of follow-up. Finally, raters took into account all active psychiatric symptoms and the overall level of psychosocial adjustment to assign a Global Assessment Scale (GAS)(6) score.

In the following analyses, group A had major depression and no panic attacks within the present episode. For group B, the hierarchical rule was suspended; probands in this group met the full definition for major depression but also, within the present episode, had experienced panic attacks sufficient in number and severity to otherwise meet criteria for definite panic disorder (at least one panic attack per week for at least 6 weeks). Patients in group C had a lifetime diagnosis of panic disorder and were in an episode of major depression when they entered the study; they were not required to have a minimum number of panic attacks within the index depressive episode. Excluded from this analysis were patients who had had one panic attack per week for less than 6 weeks within the index episode of major depression. Patients in group A and group B might have had panic attacks outside of depressive episodes, but they were insufficient in number to meet the RDC for panic disorder. Patients in group A, in addition, might have had panic attacks in previous episodes of major depression.

All patients in group C were in an episode of secondary depression at intake, although some might have previously had primary depression; that is, they might have had an episode of major depression before they ever developed panic disorder or any other nonaffective disorder. Also, some patients in group B might have had an index episode of secondary depression, since they might have had previous nonaffective illnesses other than panic disorder.

A subset of probands from the overall study, recruited to fill diagnostic cells of predetermined sizes, participated in the family study; 307, or 58.7%, of the total series of 523 patients did so. Professional raters attempted to contact and personally interview all of the 307 patients' first-degree relatives who were over the age of 16 and who were living within the continental United States. Relatives living outside a 100-mile radius of each university center (200 miles in the case of Iowa) were interviewed by telephone, and all others were interviewed in person. Raters used the SADS-Lifetime Version (4) to obtain the lifetime history of psychopathology necessary to make an RDC diagnosis.

Morbid risk figures were not age-corrected, since the three groups of relatives to be compared were almost identical in age at interview. Statistical comparisons were made across all three groups by means of an F test for continuous variables and a chi-square test for categorical ones; if more than 20% of the expected values were 5 or less, Fisher's exact test was used instead. Follow-up pairwise comparisons (chi-square without Yates' correction or Duncan's test) were made only if the three-way comparisons yielded a $p<0.05$; those pairwise comparisons are indicated as significant in tables 1, 3, 4, and 5 if p values were <0.05.

RESULTS

Family History

Of the 307 family study probands with major depression, only 11 (3.6%) met the RDC for panic disorder (group C), while another 52 (16.9%) constituted the group that had major depression with panic (group B). The remaining 244 patients had not experienced panic attacks during the index depressive episode (group A). The three groups of probands did not differ significantly in age at the first episode of major depression. The mean±SD age at the first episode of depression was 29.8±14.2 years for the patients without panic attacks (group A), 25.8±11.3 years for the patients with panic attacks (group B), and 24.6±8.7 years for the patients with panic disorder (group C).

Neither the probands nor the corresponding interviewed relatives differed significantly by age or sex across proband diagnostic groups, nor did these variables distinguish the corresponding groups of relatives. The mean±SD age of the patients at intake was 39.3±15.7 years for group A, 38.8±14.8 years for group B, and 33.4±9.3 years for group C. The mean±SD age at interview of the first-degree relatives was 40.4±16.9 years for relatives of group A, 41.4±16.6 years for relatives of group B, and 41.9±16.9 for relatives of group C. Among the probands, 139 (57.0%) in group A were female, 38 (73.1%) in group B were female, and seven (63.6%) in group C were female. Among the interviewed relatives, 506 (57.3%) of the relatives of group A probands were female, 94 (57.3%) of the relatives of group B probands were female, and 28 (62.2%) of the relatives of group C probands were female.

Only two (3.8%) of the 52 depressed patients with panic (group B) had family pedigrees that included an individual with panic disorder and at least one other relative who had major depression without panic attacks; such mixed pedigrees were not substantially less likely among the depressed probands without panic (group A) (five of 244, or 2.0%). Moreover, major depression with panic attacks was not more common among the relatives of depressed probands with panic than among the relatives of other probands (see table 1).

When compared to the depressed patients without panic, the depressed probands with panic had a somewhat higher familial loading for major and primary depression but a very similar loading for mania. In addition, the relatives of these two groups had equivalent rates of various anxiety disorders. In contrast, probands with RDC panic disorder (group C) had substantially lower familial rates of primary depression as well as significantly higher familial rates of obsessive-compulsive and phobic disorder. When these probands were compared to the other two groups pooled, their familial loading for panic disorder was also significantly higher ($p=0.022$, Fisher's exact test).

The exclusion of probands with histories of mania or hypomania had little effect on these patterns. Probands with nonbipolar illness in groups A, B, and C had relatives with morbid risks for primary depression of 22.0% (127 of 576), 30.9% (34 of 110), and 11.4% (five of 44), respectively ($\chi^2=7.6$, df=2, $p=0.023$). Corresponding rates for mania were 1.0% (six of 576), 0.9% (one of 110), and 0; the rates for panic disorder were 1.4% (eight of 576), 1.8% (two of 110), and 6.8% (three of 44) ($\chi^2=7.0$, df=2, $p=0.032$). Again, with the exception of generalized anxiety disorder, all anxiety disorders were more prevalent among the relatives of panic disorder probands than they were among the relatives of the other two proband groups. The relatives of these proband groups (A and B), in turn, had very similar risks for anxiety disorders. The only substantial change produced by removing bipolar I and bipolar II probands from the analysis concerned alcoholism: the relatives of probands who had nonbipolar depression with panic were significantly more likely to be alcoholic than were the relatives of probands who had nonbipolar depression without panic (26 of 110, 23.6%, versus 73 of 576, 12.7% ($\chi^2=9.0$, df=1, $p<0.005$), while the relatives of probands with RDC panic disorder had an intermediate risk (nine of 44, 20.5%).

Since relatively infrequent but highly loaded pedigrees may produce such findings, we repeated these analyses using numbers of families rather than numbers of relatives in the denominators (see table 1). Patterns changed little, although some comparisons no longer reached significance. Probands who had depression with panic were only slightly more likely to have a family history of depression than were depressed probands without panic. Family histories of anxiety disorders clearly distinguished the RDC panic disorder probands from the other two proband groups.

TABLE 1. Family Study Data on Depressed Probands Without Panic Attacks, Depressed Probands With Panic Attacks, and Panic Disorder Probands With Major Depression

Diagnosis	Major Depression Without Panic Attacks (Group A) (N=244)		Major Depression With Panic Attacks (Group B) (N=52)		Panic Disorder With Major Depression (Group C) (N=11)		Three-Way Comparison		Follow-Up Pairwise Comparison (chi-square or Duncan's test; df=1, $p<0.05$)
	N	%	N	%	N	%	χ^2 (or F) (df=2)	p	
First-degree relatives (interviewed)	883		164		45				
Any major depression	264	29.9	64	39.0	11	24.4	6.3	0.04	A<B
Any major depression with panic attacks	17	1.9	4	2.4	1	2.2	—	—	
Only primary depression	189	21.4	48	29.3	5	11.1	8.3	0.016	C<A, C<B
Mania	17	1.9	3	1.8	0	0.0	—	—	
Alcoholism	115	13.0	31	18.9	9	20.0	—	—	
Generalized anxiety disorder	56	6.3	17	10.4	6	13.3	6.0	0.05	
Panic disorder	11	1.2	2	1.2	3	6.7		0.01[a]	A<C
Obsessive-compulsive disorder	3	0.3	0	0.0	2	4.4		0.02[a]	A<C, B<C
Phobic disorder	33	3.7	9	5.5	9	20.0	25.7	0.001	A<C, B<C
Phobic disorder without panic	29	3.3	7	4.3	6	13.3	11.8	0.002	A<C, B<C
Any anxiety disorder	94	10.6	24	14.6	12	26.7	11.8	0.003	A<C, B<C
Families									
Any major depression	150	61.5	36	69.2	3	27.3	6.8	0.03	
Any major depression with panic attacks	15	6.1	4	7.7	1	9.1	—	—	
Only primary depression	122	50.0	30	57.7	2	18.2	—	—	
Mania	12	4.9	3	5.8	0	0.0	—	—	
Alcoholism	85	34.8	20	38.5	6	54.5	—	—	
Generalized anxiety disorder	18	7.4	5	9.6	2	18.2	—	—	
Panic disorder	11	4.5	2	3.8	3	27.3		0.001[a]	A<C, B<C
Obsessive-compulsive disorder	3	1.2	0	0.0	1	9.1	—	—	
Phobic disorder	23	9.4	5	9.6	4	36.4	8.2	0.025	A<C
Phobic disorder without panic	23	9.4	5	9.6	4	36.4	8.2	0.025	A<C

[a] By Fisher's exact test.

Diagnostic Subtype and Phenomenology

Depressed patients with panic attacks had been depressed significantly longer at intake (mean±SD= 88.9±118.5 weeks) than depressed patients without panic attacks (50.9±75.6 weeks) (pairwise Duncan follow-up test, $p<0.05$). Although panic disorder patients were less impaired in their relationships with friends, there were no consistent patterns to suggest that one group was more impaired than the others. Nevertheless, the presence of panic attacks appeared to indicate a relatively severe depression, since, without exception, individual depressive symptoms, both endogenous and nonendogenous, were more severe among group B patients than they were among patients in group A (see table 2).

Patients who had depression with panic were significantly less likely to have had simple depression at intake but significantly more likely to have had endogenous or agitated depression (table 3). RDC panic disorder patients were also significantly more likely than depressed patients without panic attacks (group A) to have had agitated depression and significantly less likely to have had simple depression. However, the latter difference was tautological given the RDC definition of simple depression ("episodes that develop in a person who has shown no significant signs of psychiatric disturbance in the year prior to the development of the current episode, with the exception of symptoms associated with either major or episodic minor depressive disorder, manic or hypomanic disorder").

Course and Outcome

Two-year follow-ups were completed for 469 (90.0%) of the 523 probands who entered the larger study. Depressed patients with panic experienced significantly higher levels of depressive symptoms during the final 6 months of the 2-year follow-up, were significantly less likely to have recovered from the index depressive episode, and were at least somewhat more likely to show impairment in each of the psychosocial areas of functioning we considered than were the depressed patients without panic (table 4). RDC panic disorder patients consistently had the worst outcomes, although they differed significantly from the depressed patients with panic on only one outcome measure, the proportion with work impairment. These findings were also essentially unchanged after removal of the data of bipolar I and bipolar II patients from the analysis.

Differences in treatment experiences apparently did not account for these findings. The three diagnostic

TABLE 2. Differences in Baseline Severity of Depressive Symptoms in 91 Depressed Patients With Panic Attacks and 417 Depressed Patients Without Panic Attacks

Symptom	Significance of Difference in Symptom Severity Between Groups (p)[a]
Endogenous	
Distinct quality of mood	n.s.
Guilt	0.006
Terminal insomnia	0.02
Anorexia	0.04
Weight loss	n.s.
Anhedonia	0.004
Agitation	0.002
Retardation	n.s.
Morning dysphoria	n.s.
Lack of reactivity	0.0001
Other	
Dysphoria	0.0001
Negative self-evaluation	0.001
Suicidal tendencies	n.s.
Difficulties with concentration	0.01
Fatigue	0.01
Initial insomnia	n.s.
Weight gain	n.s.
Increased appetite	n.s.
Hypersomnia	n.s.

[a] All symptoms were more severe in the group with major depression with panic attacks (group B). Comparisons were made by t tests.

groups did not differ significantly in the proportions of patients who received vigorous tricyclic, lithium, antipsychotic, or ECT trials (as defined in the Method section) during the first 2 months of follow-up, nor did they differ in the proportions receiving these therapies after 1 year.

DISCUSSION

Panic attacks, when they occurred only within depressive episodes, were not associated with significant increases in familial loading for anxiety disorders, primary depression, or mania, although the overall risk for major depression was increased somewhat. The group with RDC panic disorder, on the other hand, exhibited a significantly lower familial loading for primary affective disorder and a substantially higher one for the major anxiety disorders. These findings do not support the single-disorder, continuum model we described at the beginning of this paper.

Depression with anxiety did not breed true, nor were depressive and anxiety disorders more likely to coexist in the family pedigrees of probands who had depression with anxiety. These findings weigh against assertions that such patients suffer from two separate but coexisting disorders or from a third separate illness. In composite, the family study data support only the remaining hypothesis, that a patient who presents with panic attacks and a depressive syndrome probably has one of two separate disorders.

There are both similarities and differences between these results and those of two other relevant studies (table 5). As we did in the present study, Leckman et al. (7) and VanValkenburg et al. (8) found the highest risk for major depression among the relatives of probands with major depression complicated by prominent anxiety symptoms. Unlike the present study, Leckman et al. (9) found that this increased risk extended to relatives of probands whose anxiety syndromes had occurred outside of depressive episodes. Moreover, in neither of these earlier studies did the temporal relationship of anxiety symptoms to depressive episodes predict familial loading for anxiety disorders.

Methodological factors may well account for these differences. VanValkenburg et al. (8) assessed all relatives indirectly through interviews with the probands, and direct interviews were available for only 40.0% of the relatives considered at risk in the Leckman et al. study (7). The family history approach is, in fact, probably adequate when groups are compared by risks for such broad categories as mania, major depression, alcoholism, and schizophrenia. Using diagnoses based on direct interviews as a standard, the family history method has yielded assessments with low sensitivity but high specificity for these broad diagnostic categories (10). It has not been established that the family history method as accurately identifies anxiety disorders, and, given the symptom overlap we have described, it is highly doubtful that this method adequately separates relatives with primary depression from those with primary anxiety disorders. Therefore, the family study approach is necessary to answer the questions we posed previously. With our use of such a design, the present study supports the hierarchy of major depression over panic disorder.

Moreover, because the probands described by Leckman et al. were drawn from a community survey, not only were the temporal relationships between depression and anxiety syndromes based on retrospective accounts, but the lifetime diagnosis of major depression itself depended, in most cases, on recall by the subjects. The presence of major depression in the present study was much more certain, since the subjects were currently in an episode and were seeking treatment for it. Panic attacks may, in fact, mark a more severe and genetically significant depression than cases at the milder end of the severity spectrum, such as those described by Leckman et al. (7). If this is so, then the impact of panic attacks on familial loading should be less apparent when the question of "caseness" is less in doubt, as in the present study.

Although the family study data failed to clearly separate major depression with current panic attacks from major depression without current panic attacks, these groups of patients nevertheless appeared to differ in meaningful ways. First, patients with panic attacks suffered a more symptomatically severe depression; not only were they more likely to have an endogenous or agitated depression, but each individual depressive symptom was at least somewhat more severe on average than it was in the patients without panic attacks.

TABLE 3. Subtypes of Major Depression in Depressed Patients Without Panic Attacks, Depressed Patients With Panic Attacks, and Panic Disorder Patients With Major Depression

Subtype of Depression in Index Episode	Major Depression Without Panic Attacks (Group A) (N=417)		Major Depression With Panic Attacks (Group B) (N=91)		Panic Disorder With Major Depression (Group C) (N=15)		Three-Way Comparison		Follow-Up Pairwise Comparison (chi-square; df=1, $p<0.05$)
	N	%	N	%	N	%	χ^2 (df=2)	p	
Bipolar I	70	16.8	10	11.0	1	6.7	—	—	
Bipolar II	46	11.0	9	9.9	0	0	—	—	
Nonbipolar	301	72.2	72	79.1	14	93.3	—	—	
Primary	280	67.2	46	50.5	1	6.0	—	—	
Recurrent	184	44.1	44	48.4	11	73.3	—	—	
Psychotic	54	12.9	13	14.3	2	13.3	—	—	
Incapacitated	59	14.1	15	16.5	3	20.0	—	—	
Endogenous	245	58.7	69	75.8	8	53.3	9.6	0.008	A<B
Agitated	103	24.7	32	35.2	8	53.3	9.4	0.009	A<B, A<C
Retarded	132	31.6	33	36.3	7	46.7	—	—	
Situational	113	27.1	26	28.6	5	33.3	—	—	
Simple	184	44.1	22	24.2	0	0	22.5	0.0001	B<A, C<A, C<B

TABLE 4. Outcome After 2 Years for Depressed Patients Without Panic Attacks, Depressed Patients With Panic Attacks, and Panic Disorder Patients With Major Depression

Variable	Major Depression Without Panic Attacks (Group A) (N=374)		Major Depression With Panic Attacks (Group B) (N=81)		Panic Disorder With Major Depression (Group C) (N=14)		Three-Way Comparison		Follow-Up Pairwise Comparison (chi-square or Duncan's test; df=1, $p<0.05$)
	N	%	N	%	N	%	χ^2 (df=2)	p	
Recovered from index episode[a]	322	86.1	61	75.3	10	71.4	7.3	0.03	B<A
Recovered from both major depression and panic disorder at 2-year follow-up[b]	277	74.1	48	59.3	7	50.0	10.0	0.01	A>B, A>C
Work impairment[c]	74	28.7	14	28.0	8	66.7	8.0	0.02	A<C, B<C
Impaired relationship with spouse[d]	60	35.9	19	50.0	6	66.7	—	—	
Impaired relationships with friends	166	44.4	43	53.1	8	57.1	—	—	
Impaired sexual relations	101	27.0	24	29.6	7	50.0	—	—	
Impaired contentment or general satisfaction	186	49.7	46	56.8	11	78.6	—	—	
Overall psychosocial impairment, by rater's assessment	212	56.7	50	61.7	12	85.7	—	—	

[a] Mean±SD number of depressive symptoms during the last 6 months of follow-up: group A, 1.9±1.2; group B, 2.4±1.5; group C, 2.5±1.5; three-way comparison: $F=6.3$, df=2, $p=0.003$ (A<B).

[b] Mean±SD GAS score after 2 years: group A, 65.2±16.0; group B, 61.0±19.2; group C, 56.6±13.3; three-way comparison: $F=3.7$, df=2, $p=0.03$ (C<A).

[c] For this variable, N=258 for group A, N=50 for group B, and N=12 for group C.

[d] For this variable, N=167 for group A, N=38 for group B, and N=9 for group C.

VanValkenburg et al. (8) also compared depressed patients with and without panic attacks according to the presence of 13 depressive symptoms and found that 10 of these were more common in the former group, eight significantly so.

Perhaps as a reflection of this relative severity, our depressed patients with panic attacks were also less likely to recover during the 2-year follow-up period than were those without panic attacks. VanValkenburg et al. noted this as well, and in their follow-up of unspecified duration, they found that 61.0% of 23 depressed patients with panic attacks had a "poor psychosocial outcome," compared to only 10.0% of the depressed patients who were free of panic attacks.

These findings invite analogies between panic attacks and delusions. Like panic attacks, delusions, when present, are associated with greater baseline severity in individual depressive symptoms (11-13) and with a poorer short-term prognosis (14-16). Moreover, patients who develop an affective syndrome only after a lengthy period of delusions have, in most systems, a diagnosis that reflects the nature of the delusions (i.e., schizophrenia or paranoid disorder) rather than the type of affective syndrome (i.e., major depression). If delusions occur only within episodes of major depression or mania, the affective symptoms are

TABLE 5. Data From Two Studies of Familial Psychopathology Among Probands With Major Depression Without Anxiety, Major Depression With Anxiety, and Anxiety With Depression

	Proband Diagnosis			Three-Way Comparison		Follow-Up Pairwise Comparison (chi-square; df=1, p<0.05)
Variable	Depression Without Anxiety[a]	Depression With Anxiety[b]	Anxiety With Depression[c]	χ^2 (df=2)	p	
Leckman et al. study (7, 9)						
Number of probands	23	51	30	—	—	
Number of relatives at risk	308	337	165	—	—	
Percent of relatives with major depression	10	19	17	10.0	0.001	A<C, A<B
Percent of relatives with anxiety[d]	9	14	15	—	—	
VanValkenburg et al. study (8)						
Number of probands	42	23	31	—	—	
Percent of families with major depression	31	35	13	—	—	
Percent of relatives with anxiety states[e]	7	22	29		0.05[f]	A<C

[a] Equivalent to group A in the present study.
[b] Anxiety syndromes occurred only within depressive episodes; equivalent to group B in present study.
[c] Anxiety syndromes occurred outside of depressive episodes; equivalent to group C in present study.
[d] "Anxiety" includes RDC agoraphobia, other phobias, panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder.
[e] "Anxiety states" includes *DSM-III* panic disorder.
[f] By Fisher's exact test.

emphasized for diagnostic purposes, just as, in most systems, affective symptoms preempt anxiety symptoms when these two features only appear together.

As with panic disorder and depression, there has been controversy about whether predominantly delusional states and predominantly affective ones constitute two illnesses or different manifestations of only one. The boundary between affective disorder and schizophrenia has been the source of a similar though much more extensive controversy. For instance, the proposal by Weissman et al. (17) that patients with both anxiety and depressive symptoms have a "shared diathesis" has precedence in earlier proposals regarding the nature of schizoaffective disorder.

Such boundary problems have traditionally generated much discussion and many diagnostic revisions, but little lasting consensus. This is due in part to the complexity and number of alternative hypotheses applicable to these problems. It is probably due as well to shifting diagnostic conventions and the limited power of any single validator to highlight actual group differences. This lends importance to suggestions which might promote consensus on comorbidity issues. First, any diagnostic revision, whether adopted by an individual investigator or on a broader scale, should be supported by at least several independent studies showing that this revision increases validity. Revisions are otherwise useful, of course, as long as results that are obtained by using a conventional grouping are presented as well, so that independent replication is possible. Second, studies directed at comorbidity issues should, whenever possible, use two or more types of validators, e.g., family study and follow-up data, follow-up and biological marker data, or phenomenological clustering and follow-up data. This would promote a research literature that would be valuable for testing the usefulness of given validators as well as the appropriate position of boundaries between disorders.

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Dissociation and Hypnotizability in Posttraumatic Stress Disorder

David Spiegel, M.D., Thurman Hunt, B.S., and Harvey E. Dondershine, M.D., J.D.

The authors compared the hypnotizability of 65 Vietnam veteran patients with posttraumatic stress disorder (PTSD) to that of a normal control group and four patient samples using the Hypnotic Induction Profile. The patients with PTSD had significantly higher hypnotizability scores than patients with diagnoses of schizophrenia (N=23); major depression, bipolar disorder—depressed, and dysthymic disorder (N=56); and generalized anxiety disorder (N=18) and the control sample (N=83). This finding supports the hypothesis that dissociative phenomena are mobilized as defenses both during and after traumatic experiences. The literature suggests that spontaneous dissociation, imagery, and hypnotizability are important components of PTSD symptoms.

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Defense mechanisms have received attention largely from the retrospective vantage point of psychoanalysis. They have been viewed as defenses against painful memories rather than painful experiences, and the reasons for the use of one particular defense mechanism rather than another have always been rather mysterious (1). More recently, attention has been directed toward the function of defense mechanisms as a protection against the overwhelming experience of trauma as it is inflicted. Individuals capable of profound dissociation and the analgesia associated with high hypnotizability might well mobilize such defenses during an episode of physical trauma. One example is the out-of-body experience often reported by women during rape or by patients suffering cardiac arrest. They describe the sensation of floating above their own bodies, feeling strangely detached from and even sorry for the person suffering beneath them.

Dissociation has been reported during many traumatic experiences (2). It may be that spontaneous reliving rather than simply remembering a traumatic event in posttraumatic stress disorder (PTSD) owes some of its hypnotic-like abreactive intensity to the fact that the patient was in a dissociated state during the trauma and is thus in a similar mental state while reliving it. Dissociation then becomes a defense against the painful affect associated with memories of the traumatic experience. Such abreactions can be elicited by a variety of stimuli, such as a tape recording of combat noises (3) and formal hypnotic age regression (4, 5), which reactivate the dissociative response to the trauma.

The importance of imagery in posttraumatic symptoms has recently been observed (6). Theories about traumatic symptoms differ; some emphasize cognitive breakdown and withdrawal, with amnesia as a focal symptom (4, 7), while others emphasize intrusive recollections and images (8). The *DSM-III* criteria include both types of symptoms: numbing of responsiveness on the one hand and intrusive recollections, sudden reliving of the traumatic events, and stimulus sensitivity on the other. Both observations may be fundamentally correct. What may occur in response to trauma is a polarization of experience in which trauma victims alternate between intense, vivid, and painful memories and images associated with the traumatic experience and a kind of pseudonormality in which the victims avoid such memories, using traumatic amnesia, other forms of dissociation, or repression, with a reduction in adaptive capacity and a constriction of the range of affective response. This polarization of consciousness can be seen in the hypnotic state, during which intense absorption in the hypnotic focal experience (9) can be achieved by means of the dissociation of experience at the periphery of consciousness (10, 11). As in the hypnotic experience, traumatic imagery is either intense or absent. Thus, more frequent use of dissociative defenses, with their on-off quality, would be especially likely among victims of severe trauma.

A survey of the types of traumatic near-death experiences reveals a number of experiences that are dissociative in nature and resemble typical hypnotic phenomena: time distortion, visual hallucinations, and

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other sensory alterations (12–14). The presence of PTSD-related auditory hallucinations in nonschizophrenic patients has been shown to be related to the intensity of combat exposure and PTSD symptoms (15). These hallucinations generally took the form of voices of dying comrades, enemy soldiers, or civilians. These voices often suggested that the patient should commit suicide. The authors observed that such patients were especially sensitive to an imaginal flooding technique which recreated the state of physiological arousal experienced in combat (3). The relevance of hypnotic phenomena to the experience of trauma is also supported by reports of the usefulness of hypnosis to facilitate treatment of PTSD symptoms by enhancing such techniques as abreaction with modification of the details of the traumatic experience (4), grief work using hypnotic images (5), and hypnotic alteration of combat dreams (16).

The relationship between dissociation and trauma has had little empirical validation, in part because of the comparatively few studies of the association between the related construct of hypnotizability and trauma (2, 17–19) and the absence, until recently, of measures of dissociation per se (20). The clinical use of hypnotizability testing can be helpful to differential diagnosis, since it can evoke and measure dissociation. Those who are hypnotizable often use the capacity spontaneously (8, 21). Breuer (22), in fact, described dissociation as a "hypnoidal" state: "What we should be doing would be first to assign the phenomena of hysteria to hypnosis, and then to assert that hypnosis is the cause of those phenomena" (p. 248). Hypnotizability, which is the fundamental capacity to experience dissociation in a structured setting, should be high if extreme dissociative symptoms such as amnesia, fugue, hysterical psychosis, or multiple personality disorder occur (2, 23, 24). Thus, it can be helpful diagnostically to use a measure of hypnotizability (25, 26), such as the Hypnotic Induction Profile (9) or the Stanford Hypnotic Clinical Scale (27), in the differential diagnosis of dissociative disorders.

In one study of hypnotizability in PTSD (28), 26 Vietnam combat veterans were divided into high and low symptom groups on the basis of posttraumatic symptoms, and those with high symptoms were found to be significantly more hypnotizable on the Stanford Hypnotic Susceptibility Scale, Form C (29). While no inference of cause and effect can be made, Hilgard (30) observed that self-report of punishment during childhood was one of three variables which were associated with later high hypnotizability in a population of normal college students ($r=0.30$, $N=187$). She speculated: "A possible tie between punishment and hypnotic involvement might come by way of dissociation . . . . Although we have no direct evidence, some of our case material . . . suggests that reading or other involvements may sometimes be an escape from the harsh realities of a punitive environment" (p. 221). When Frischholz (31) reanalyzed these data, he found that a multiple correlation combining imaginative involvement and punishment yielded a significantly higher correlation with hypnotizability ($r=0.40$) than did either variable alone. This suggests that the two variables (and presumably others) contribute independently to the development or preservation of hypnotizability.

The finding of higher hypnotizability among individuals with PTSD contrasts with the findings of generally lower hypnotizability and the absence of very high hypnotizability among patients with other severe psychiatric disorders, such as schizophrenia (32–34) and affective disorders (34, 35). On the basis of these findings and the prominence of dissociative symptoms in PTSD, we predicted that patients with PTSD should have higher hypnotizability scores than other patient samples and a normal control sample.

METHOD

The 65 patients in the posttraumatic stress disorder sample represented half of a consecutive series of inpatients randomly assigned to one of two programs at the Menlo Park Division of the Palo Alto Veterans' Administration Medical Center designed for the treatment of this disorder in veterans who had served in Vietnam. All met *DSM-III* criteria for PTSD, and their hypnotizability was assessed by one of us (H.E.D.) on the day of admission using the protocol for the Hypnotic Induction Profile (10). The other subject groups were derived from a sample of normal volunteers ($N=83$) and in- and outpatients, primarily at the same medical center, who have been described previously (34). Informed consent for participation in the study was obtained from all subjects; only one patient refused. The comparison patients had diagnoses of schizophrenia ($N=23$); generalized anxiety disorder ($N=18$); major depression, bipolar disorder—depressed, and dysthymic disorder ($N=56$); and miscellaneous disorders ($N=18$). Hypnotizability scores were taken from the induction score of the Hypnotic Induction Profile. This scale is a 0–10 linear measure consisting of scores on five equally weighted items: dissociation, challenged hand levitation, an experience of reduced control in one hand, response to the cutoff signal, and instructed sensory alteration.

The data analytic technique was analysis of covariance with age as the covariate (time since latency has been shown to be inversely related to hypnotizability [10, 36]), followed by post hoc t tests where permitted.

RESULTS

The mean ± SD hypnotizability score for the patients with PTSD was 8.04 ± 2.24. These patients had a mean induction score significantly higher than that of all the other patients and control subjects taken as a group ($t=11.9$, $df=261$, $p<0.001$). Their hypnotizability

TABLE 1. Hypnotic Induction Profile Scores for Patients With PTSD, Control Subjects, and Patients With Other Psychiatric Diagnoses

				Hypnotic Induction Profile				
		Age (years)		Score		Comparison With Mean Score of PTSD Patients[a]		
Group	N	Mean	SD	Mean	SD	t	df	p
Patients with PTSD	65	34.9	4.0	8.04	2.24			
Normal control subjects	83	28.1	8.8	7.23	2.24	2.48	146	0.01
Patients with schizophrenia	23	35.7	10.4	3.99	3.19	6.26	86	0.001
Patients with generalized anxiety disorder	18	38.8	12.2	4.06	3.30	5.39	81	0.001
Patients with affective disorders	56	43.1	13.1	5.76	3.19	3.83	19	0.001
Patients with miscellaneous disorders	18	37.4	14.2	5.96	2.85	2.80	81	0.01

[a] Analysis of covariance indicated a significant main effect for diagnosis ($F=12.3$, $df=1, 5$, $p<0.001$). Significance values are from post hoc t tests.

score was significantly higher than that of each of the other groups (see table 1). There was a significant main effect for age ($F=7.17$, $df=1, 256$, $p<0.008$), but this did not account for the differences observed. A simple analysis of variance yielded significance values of the same magnitude, ruling out problems of colinearity in the analysis of covariance due to age differences.

DISCUSSION

Our findings are consistent with the hypothesis that many of the symptoms of posttraumatic stress disorder are dissociative in nature. This sample of Vietnam veterans with PTSD had higher hypnotizability scores than a normal control sample, and their scores were substantially higher than those of all the other psychiatric patient groups, including those with schizophrenia, dysthymia, major and bipolar depressive disorders, and generalized anxiety disorder. Thus, despite being quite symptomatic, patients with PTSD had hypnotizability scores more like those of the normal control sample than any of the other patient groups. Indeed, their scores were higher than normal and twice those of the small sample of patients with generalized anxiety disorder, which suggests the prominence of dissociative as opposed to anxiety-related symptoms in PTSD. Further, while age was found in this study, as in previous studies (10, 36), to be correlated inversely with hypnotizability, the differences held when the effect of age was partialed out of the analysis.

The present study differs from previous work by Stutman and Bliss (28) in that we measured a large patient sample who had sought treatment, whereas the earlier investigators studied a community sample of veterans responding to a newspaper advertisement, finding that those high in the symptoms of posttraumatic stress disorder were more highly hypnotizable than those who were low in such symptoms. Clearly, the two studies are compatible, and, indeed, the Stutman and Bliss finding (28) provides evidence that it is not merely self-selection in seeking treatment that accounts for the high hypnotizability observed, but rather the prominence of PTSD symptoms.

Most of the symptoms associated with posttraumatic stress disorder in *DSM-III* have a flavor of dissociation: reexperiencing the event through intrusive recollections, nightmares, flashbacks, emotional numbing with feelings of detachment or isolation, stimulus sensitivity with the avoidance of environmental cues that are associated with recollections of the traumatic events, and difficulty concentrating. The phenomenon of dissociation implies an isolated set of interacting affects and memories that can be reactivated. They come as a unit, consistent with evidence in cognitive psychology for state-dependent memory (37). This body of work has shown that mental content can be more accurately retrieved when the mood state is congruent in the retrieval process to that in which the material was learned. Memories laid down in the company of strong affect might therefore be available only if the person were able to tolerate reexperiencing the associated intense affect. Such experiences are defensively avoided, and thus the memories and their association networks of affect are dissociated.

The study of dissociation began with observations of overlapping phenomena in hypnosis and multiple personality disorder patients (38). Hysterical patients prone to dissociative symptoms have been found to be highly hypnotizable (2, 39) and are likely to use their dissociative capacities in the face of stress: "Hysterical patients . . . have an exaggerated, perhaps inborn, tendency toward mental dissociation that provides them with a ready-made mechanism of defense for dealing with emotionally painful events" (39, p. 947). Janet (40) emphasized dissociation as the primary defense, while Freud (41) acknowledged dissociation but emphasized repression. The major distinction between the two defense mechanisms can be understood in terms of the relationships among the material that is kept out of conscious awareness. In dissociation, specific memories and associated feelings seem to contain rules excluding other memories and feelings from conscious awareness, although these rules are not absolute, and the boundaries can be breached (31). For example, memories associated with depressive affect tend to prevent recall of happier memories (37). In repression, similar material may be kept out of awareness to exclude uncomfortable affects that accompany it, but there is no rule within one set of memories or associations which necessitates the exclusion of others. Many PTSD patients consider their memories to be incompatible with conducting an ordinary life and rewarding relationships. These two jarringly different images of the self must be kept apart. As Hilgard (11) has noted, dissociated mental states can be thought of as coexisting side by side, separated by amnesic barriers, while repression implies a more vertical or archeological mental structure.

Freud (41) was troubled about the relationship between traumatic neuroses and his general theory that repression served as a means of keeping unacceptable wishes out of consciousness. Why would trauma be repressed when it was not wished for? His repression model fits the development of oedipal fears and wishes better than it does trauma. Much has recently been made of Freud's abandonment of the trauma theory as the general explanation for the neuroses. The possibility that different defenses are mobilized by trauma and by developmental problems is of greater interest. Dissociation may be elicited more by physical trauma, repression by longstanding developmental conflicts and warded-off wishes.

Trauma can be understood as the experience of being made into an object, a thing: the victim of someone else's rage, of nature's indifference, of one's own physical or psychological limitations. Along with the pain and fear that are associated with rape, combat trauma, or natural disaster comes an overwhelming and marginally bearable sense of helplessness, a realization that one's own will and wishes become irrelevant to the course of events; this leaves a view of the self that is damaged or contaminated by the humiliation, pain, and fear that the event imposed or a fragmented sense of self. The preexisting personality attempts to carry on as though nothing at all had happened. However, the need for the dissociation implies an association: that pain and humiliation were, in fact, inflicted. Thus, the person reconsolidates with a sense of fragmentation, and the real truth is the dissociated and warded-off self that was humiliated and damaged.

Thus, while dissociation serves the function of defending consciousness from the immediate experience of painful events—physical pain, fear, anxiety, and helplessness—it then becomes an entrenched part of the overall view of self. Once the self is divided in a powerful way, the experience of unity becomes problematic, since ordinary self-consciousness is no longer synonymous with the entirety of self and personal history. Rather, it becomes associated with the awareness of some warded-off tragedy, the moment of humiliation and fear, the act of cowardice, the sense of having been degraded. The person comes to feel that there is an inauthentic self which carries on the everyday functions of life but with the sense of numbing, the lack of genuine pleasure in otherwise pleasurable activities. The unconscious, warded-off memories exert censorship on conscious experience. The process of dissociation becomes part of the patient's identity, to be remobilized in the face of subsequent stress or even imagined situations reminiscent of this stress.

The experience of involuntariness may be a link among hypnosis, dissociation, and trauma. The importance of involuntariness in hypnosis was emphasized originally by Bernheim (42) and more recently by Weitzenhoffer (43). As discussed earlier, the kinds of events that mobilize dissociation as a defense also seem to be those in which the patient's volition is physically overridden. Thus, the natural involuntariness associated with the hypnotic state can be viewed as a repetition of an experience in which involuntariness is literally imposed by external circumstances.

The causal explanation for these findings remains obscure. Does the experience of trauma enhance hypnotizability, or are highly hypnotizable individuals more sensitive to the aftereffects of combat trauma? It is unlikely that individuals with low hypnotizability are impervious to the effects of combat. It may be that they assimilate the experience less symptomatically by maintaining their perspective on it as an external force imposed on them, thereby minimizing damage to their self-esteem. Or perhaps they develop other symptoms, such as alcohol and drug abuse, which may overshadow the intrusive recollections and other symptoms of PTSD. It would be interesting to see whether veterans with PTSD have drug and alcohol abuse rates that are lower than those of veterans with similar combat exposure but without PTSD. It is also possible that the experience of extreme physical violence is so psychologically devastating that equally extreme defenses are mobilized to deal with the experience. Such trauma may stimulate or reopen access to this form of dissociative experience, which normally begins to decline after latency (10, 36). It is possible that combat and other forms of extreme trauma create a dissociative state which is reexperienced when the content and affect of the memories are retrieved. In any event, this and previous work lend credence to the importance of dissociation as an underlying factor in the symptoms of posttraumatic stress disorder and of hypnosis as a relevant modality in the treatment of these individuals.

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Phenelzine Versus Imipramine in the Treatment of Probable Atypical Depression: Defining Syndrome Boundaries of Selective MAOI Responders

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Sixty patients with probable atypical depression—defined as meeting Research Diagnostic Criteria for depressive illness, having reactive mood, and having one of four associated symptoms (hyperphagia, hypersomnolence, leaden feeling, and sensitivity to rejection)—took part in a study contrasting phenelzine, imipramine, and placebo. Phenelzine was found to be superior to imipramine and placebo. These results were compared to results from a sample of 120 patients with identical characteristics, except that they had more than one associated atypical symptom (full atypical syndrome). The size of the drug effect was comparable in patients with full atypical and partial atypical syndromes.

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In most previous drug trials, tricyclic treatment has proved consistently superior or equal to monoamine oxidase inhibitor (MAOI) treatment (1–9). Therefore, identification of patients who preferentially improve with MAOI treatment might help delineate a depressive syndrome whose pathophysiology may be distinct. We have demonstrated that patients with reactive mood and at least two of four associated features, constituting a symptom pattern known as atypical depression, showed greater improvement with phenelzine than with imipramine or placebo (10). The four associated symptoms studied were hyperphagia, hypersomnolence, leaden feeling, and sensitivity to rejection (defined in Method). Recognizing that a requirement of two associated features was arbitrary, we expanded our study, in order to help define the syndrome boundaries, to include all patients who had reactive mood. Reactive mood and two or more associated features defined a definite atypical depression. Reactive mood and one associated feature defined probable atypical depression.

When we began our research, the literature described a heterogeneous patient population that appeared to benefit from MAOIs (11–16). There appeared to be at least two patient types: the V type, with vegetative symptoms such as hypersomnia, hyperphagia, lethargy, and reversed diurnal variation, and the A type, in which depressive symptoms, as well as anxiety, panic, and phobia, were present (12). However, it was not always clear that depressive symptoms were present, since one group of researchers stated, "Often the original depressive symptoms have become masked by phobic anxiety" (13). Patients with phobic anxiety and panic disorder uncomplicated by associated atypical symptoms clearly benefit from tricyclic antidepressants (17–19). Secondary depression is common in this group, and it may be difficult to determine which disorder is primary. Including A type patients without the associated atypical symptoms in a study contrasting MAOIs and tricyclic antidepressants might obscure a selective effect of MAOIs in hyperphagic and hypersomnolent depressed patients. This may explain the failure of other studies to identify a group that benefits more from MAOIs than from tricyclics.

In developing criteria for defining a patient group that might selectively benefit from MAOIs, we were influenced by Klein et al.'s description of a group referred to as hysteroid dysphoric patients (20). When rejected in a romantic context, these patients develop depressive episodes characterized by lethargy, oversleeping, and overeating that preferentially responded to MAOIs. It was our impression that some hypersomnolent and hyperphagic depressed patients were not characterized by hysteroid dysphoria but also selec-

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tively benefited from MAOIs. The two syndromes share similar symptoms, but the patients with atypical depression lack the narcissism, the romantic preoccupation, and the link between depression and disappointment in love relationships that characterize patients with hysteroid dysphoria. Therefore, we thought that the combination of reactive mood and the associated atypical symptoms predicted selective MAOI effect. Some patients also had a history of spontaneous panic attacks. Patients with atypical symptoms and panic attacks were included in the study but were randomly assigned to study groups separately from those who only had atypical symptoms in order to assess the role of each symptom group in predicting response to MAOIs.

This is a preliminary report on an ongoing study whose goal is to define the boundaries of atypical depression (selective MAOI responders). For contrast, we used data on 120 patients with definite atypical depression (21). The questions we asked were: Will patients with probable atypical depression selectively benefit from MAOIs compared to tricyclics or placebo? Does a history of panic attacks increase the drug effect size in this patient group?

METHOD

The study procedures, including dose of drugs, rating scales, biochemical measures, and reliability assessment were identical to those described in the study of patients with definite atypical depression (21). Therefore, only a brief review of the method is given. Patients included in the study gave written informed consent and met the following criteria.

1. Met Research Diagnostic Criteria (RDC) for major, minor, or intermittent depression.
2. Maintained mood reactivity while depressed.
3. Exhibited one of the following: increased appetite or weight gain while depressed (defined as present if appetite markedly increased or there was at least a 10-pound weight gain), oversleeping (sleeps at least 10 hours per day), severe fatigue that created a sensation of leaden paralysis or extreme heaviness of arms or legs (defined as present if marked decrease in energy or heaviness of limbs was a prominent symptom), and sensitivity to rejection as a trait throughout adulthood (defined as present if rejection resulted in depression with functional impairment, e.g., the subject missed work or school).
4. Were between 18 and 65 years of age.
5. Had no other axis I diagnoses.
6. Had had no treatment with 45 mg/day or more of phenelzine sulfate (or an equivalent MAOI) or more than 150 mg/day of imipramine hydrochloride (or equivalent tricyclic) for 2 or more weeks during the current episode.

Those with a lifetime history of at least one spontaneous panic attack (RDC) were judged panic positive.

The study consisted of two double-blind 6-week phases preceded by a 10-day single-blind placebo period. Patients who responded (see definition below) to the single-blind placebo were removed from the study. At the end of the first 6-week phase, nonresponders were removed from the study. Responders continued in the study for the second double-blind 6-week phase. The rationale for the second 6-week phase stemmed from our concern that in a population characterized by reactive mood, some improvement might be transient. It was anticipated that the second 6-week phase would identify persistent, clinically relevant improvement. The double-blind procedure and dose of medicine were identical to that previously reported. The imipramine dose was raised on a fixed schedule to 200 mg/day and phenelzine to 60 mg/day; in nonresponders the doses were raised to 300 mg/day and 90 mg/day, respectively, in the fifth and sixth weeks.

The Clinical Global Impression (CGI) scale, Hamilton Rating Scale for Depression, the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C), and the Hopkins Symptom Checklist (SCL-90) were used. A scale with definitions and specific anchors especially designed to assess reactive mood and atypical symptoms was used. Data concerning reliability have been published elsewhere (10).

A patient who remained in the study for a minimum of 28 consecutive days (out of 42) and who was given, in a random-assignment and double-blind manner, 60 mg of phenelzine, 200 mg of imipramine, or the equivalent number of placebo pills for a minimum of 14 days was considered to have completed the study.

Dropouts were divided into two types: patients for whom medication side effects led to withdrawal from the study (i.e., side-effect dropouts) and those patients who did not complete the study for reasons other than adverse drug reaction, e.g., noncompliance, substance abuse (i.e., administrative removals). These judgments were made by a rater who was blind to type of treatment.

Patients rated 1 (very much improved) or 2 (much improved) on the 7-point improvement scale of the CGI were considered to be responders. These ratings were done conservatively; only patients with a marked diminution of symptoms were rated as much improved.

Analyses involving categorical variables were done by using the uncorrected chi-square statistic or, when appropriate, Fisher's exact test. Continuous variables were analyzed by using the t test, F statistic, and analysis of covariance. Tests without a priori hypotheses were two-tailed; all others were one-tailed. Specifically, we hypothesized that both drugs would be better than placebo and that phenelzine would be superior to imipramine.

The evaluations at week 12 were done by using an end-point analysis, with the last observation carried forward. Patients who completed the 12 weeks and maintained their improvement, as well as patients judged responders who withdrew from the study at 6 weeks,

TABLE 1. Response of Patients With Probable or Definite Atypical Depression to Placebo, Imipramine, or Phenelzine Treatment

		Response at 6 Weeks					Response at 12 Weeks				
				Analysis					Analysis		
Variable	N	N	%	χ^2	df	p	N	%	χ^2	df	p
Patients with probable atypical depression	60	28	47				24	40			
Treatment											
Placebo	24	7	29				4	17			
Imipramine	19	9	47				8	42			
Phenelzine	17	12	71				12	71			
Treatment comparison											
Placebo versus imipramine versus phenelzine				6.9	2	0.03			12.1	2	0.01
Placebo versus imipramine				1.5	1	n.s.			3.4	1	0.04
Placebo versus phenelzine				6.9	1	0.01			12.2	1	0.001
Imipramine versus phenelzine				2.0	1	0.08			2.9	1	0.04
Patients with definite atypical depression	120	56	47				46	38			
Treatment											
Placebo	47	13	28				9	19			
Imipramine[a]	38	19	50				15	39			
Phenelzine	34	24	71				22	65			
Treatment comparison											
Placebo versus imipramine versus phenelzine				14.8	2	0.001			17.3	2	0.001
Placebo versus imipramine				4.5	1	0.02			4.3	1	0.02
Placebo versus phenelzine				14.7	1	0.001			17.3	1	0.001
Imipramine versus phenelzine				3.2	1	0.04			4.6	1	0.02

[a] Data for one patient were deleted.

were considered 12-week responders. Patients who were nonresponders at 6 weeks and those patients who failed to maintain their improvement from week 6 to week 12 were considered nonresponders.

RESULTS

Seventy-four patients who met the criteria for probable atypical depression were randomly assigned to medication in a double-blind manner. Eighty-one percent (N=60) completed the study. Twenty-seven were assigned to placebo, 23 to imipramine, and 24 to phenelzine. The proportion of dropouts did not vary by treatment condition ($\chi^2=2.7$, df=2, $p>0.25$). Hereafter, the discussion refers to the 60 patients who completed the study.

There were no significant differences between treatment groups in clinical or demographic characteristics at baseline. Fifty-five percent (N=33) of the sample were women, and the mean±SD age was 37.4±9.7 years. The median age at onset of probable atypical depression was 17 years. The median was used because 12 patients could not give a specific age, stating only that they had always been depressed since before age 10. Patients had had few prior hospitalizations (mean ±SD=0.1±0.5) and had a baseline Hamilton depression score of 14.2±3.4. Seventy percent (N=42) had an RDC diagnosis of major depression, 8.3% (N=5) minor depression, 36.7% (N=22) intermittent depression, and 8.3% bipolar II disorder. (Patients could receive diagnoses of both major and intermittent depressions.) This was a chronically depressed group; 40 of the 60 patients described themselves as "mostly depressed" or "almost always depressed" as adults.

At 6 weeks 29% of the placebo-treated patients, nearly half of the imipramine patients, and nearly three-fourths of the phenelzine patients were judged to be responders (table 1). The chi-square analysis involving all three groups was significant. The proportion of responders to phenelzine was greater than that for placebo, and the proportional difference between responders to phenelzine and imipramine approached significance. Outcome with imipramine was not superior to that with placebo.

Analysis of the 6-week nondichotomized CGI scores, using F and t tests, somewhat more powerfully discriminated treatment groups than the improved versus unimproved dichotomy (table 2). With the 7-point improvement scale of the CGI, the F test was significant, and on pairwise comparisons the group receiving phenelzine was superior to that receiving placebo; there was a trend for phenelzine to be significantly superior to imipramine.

The superiority of phenelzine was supported by other measures (see table 2). The phenelzine-treated group had lower scores (signifying less severe symptoms) than the placebo- and imipramine-treated groups on the SADS-C depression and extracted Hamilton depression scale measures. They also judged themselves less depressed than patients treated with placebo or imipramine (SCL-90 depression factor), as well as less anxious and less hostile.

In summary, imipramine was not superior to phen-

TABLE 2. Depression Test Scores of 60 Patients With Probable Atypical Depression After Placebo, Imipramine, or Phenelzine Treatment

	Mean Group Score at 6 Weeks			Analysis of Variance		Pairwise Comparison (p)[a]		
Measure	Placebo	Imipramine	Phenelzine	F	df	Imipramine Versus Placebo	Phenelzine Versus Placebo	Phenelzine Versus Imipramine
CGI								
Severity	3.1	2.9	2.3	2.6^b	2, 56	>0.30	<0.01	0.06
Change	3.2	2.7	2.0	5.1^c	2, 56	>0.10	<0.001	0.06
Hamilton Rating Scale for Depression	10.0	9.1	6.9	1.6	2, 51			
SADS-C[d]								
Depression	27.2	26.2	19.3	3.3^e	2, 37	>0.35	0.01	0.02
Endogenous	13.7	13.0	10.9	2.2^b	2, 37			
Anxiety	5.6	5.9	5.0	0.9	2, 37			
Extracted Hamilton scale	8.9	9.4	5.1	3.5^e	2, 37	>0.30	0.02	0.01
SCL-90								
Depression	2.6	2.4	1.8	4.4^e	2, 51	0.23	0.0050	0.01
Hostility	1.9	1.8	1.3	3.2^e	2, 51	0.33	0.02	0.03
Interpersonal sensitivity	2.3	2.2	1.8	2.8^b	2, 50	0.20	0.01	0.06
Anxiety	2.0	2.1	1.7	2.7^b	2, 50	0.23	0.05	0.02
Psychoticism	1.7	1.5	1.4	3.2^e	2, 50	0.06	0.01	0.22
Obsessive-compulsive	2.4	2.3	1.9	2.1	2, 51			
Phobia	1.6	1.6	1.4	0.5	2, 51			
Somatization	1.7	1.8	1.5	1.4	2, 51			
Paranoia	1.9	1.9	1.8	0.5	2, 51			

[a] One-tailed t test.
[b] p<0.1.
[c] p<0.01.
[d] Due to change in protocol, data were available for 41 patients.
[e] p<0.05.

elzine on any measure. On seven measures phenelzine was superior to imipramine (and placebo). Patients with reactive mood and only one associated symptom appeared to selectively benefit from phenelzine.

The mean ± SD doses of imipramine for responders and nonresponders were 277±36 mg/day and 258±53 mg/day, respectively, and plasma levels of imipramine and desipramine (mean±SD=301±193 ng/ml for responders and 475±386 ng/ml for nonresponders) were in the accepted therapeutic range (22). Similarly, the dose of phenelzine and percent inhibition of platelet MAOI were in the therapeutic range for both responders and nonresponders. The responders' mean dose of phenelzine was 74±15 mg/day, and the mean percent platelet inhibition was 80%±14%; corresponding values for nonresponders were 68±21 mg/day and 84%±7%. Failure to respond to either drug did not appear to be attributable to inadequate dose.

In the group with definite atypical depression, patients with a history of panic attacks demonstrated greater drug effect than those without such a history (21). This did not appear to be the case with patients with probable atypical depression. After 6 weeks of treatment, 60% (N=6 of 10) of the patients with probable atypical depression and a history of panic attacks were judged responders to placebo, 50% (N=5 of 10) to imipramine, and 64% (N=7 of 11) to phenelzine. In the group without a history of panic, 7% (N=1 of 14) responded to placebo, 44% (N=4 of 9) to imipramine, and 83% (N=5 of 6) to phenelzine. In this group of patients, the response rate to placebo was significantly greater for patients with a history of panic than for patients without such a history ($\chi^2=7.8$, df=1, p<0.01); there were no other differences between these two subgroups.

Response of Patients With Probable Atypical Depression at 12 Weeks

Responders at 6 weeks were continued on treatment, in a double-blind manner, for an additional 6 weeks. At 6 weeks, seven placebo patients, nine imipramine patients, and 12 phenelzine patients were judged to be responders. Of these, six placebo patients (86%), seven imipramine patients (78%), and nine phenelzine patients (75%) entered the 6- to 12-week phase. The proportions of eligible patients receiving each type of treatment who entered this phase were not statistically different. Inconvenience associated with being a study participant was usually cited as the reason for discontinuing study participation.

During the 6- to 12-week period, three of six placebo patients (50%), one of eight imipramine patients (13%), and none of nine phenelzine patients relapsed ($\chi^2=6.4$, df=2, p=0.039). The difference in the relapse rates between phenelzine- and placebo-treated patients was of trend significance.

The analysis using categorical judgments of responder and nonresponder patients was repeated at 12 weeks (table 1). This was an end-point analysis, with the last observation carried forward. The 19 patients who completed the 12 weeks and maintained their improvement and the six responders who withdrew at 6 weeks were considered 12-week responders. The 32 nonresponders at 6 weeks and the four patients who relapsed from weeks 6 to 12 were considered nonresponders. Table 1 presents data on the percents of the placebo-, imipramine-, and phenelzine-treated patients who were judged responders at 12 weeks. The chi-square analysis involving all three groups was significant, as were the pairwise contrasts of imipramine versus placebo and phenelzine versus placebo and imipramine.

Extending the study to 12 weeks eliminated some transient improvement with placebo and increased the size of the drug effect. As a result, some analyses that were only of trend significance at 6 weeks became significant at 12 weeks.

Comparison of the Two Patient Groups

Data on the 120 patients with definite atypical depression have been reported separately (21). Global clinical improvement for patients with definite and probable atypical depressions who were treated with placebo, imipramine, and phenelzine at 6 and 12 weeks are summarized in table 1. Treatment outcome as measured by physicians' global judgment was virtually the same for both patient groups at both points in treatment for phenelzine, imipramine, and placebo. Phenelzine was superior at both 6 and 12 weeks for both patient groups.

In a previous sample of 60 patients with definite atypical depression, the group receiving phenelzine had lower scores after 6 weeks of treatment on the SCL-90 factors of interpersonal sensitivity and paranoia. In this sample of 60 patients with probable atypical depression, the group receiving phenelzine had greater improvement only of trend significance in interpersonal sensitivity. Other differences on the SCL-90 measures are probably attributable to the fact that a sample size of 20 patients in each treatment group offered limited statistical power. Future analysis comparing large groups of patients with probable and definite atypical depressions will better determine which of these differences are real. At this point in these ongoing studies, treatment response offers no support for dividing patients with probable and definite atypical depressions into separate groups.

Advantage of a 12-Week Study

Relapse rates from 6 to 12 weeks for patients with probable atypical depression suggest that a 12-week study provides enhanced power by helping to identify transient improvement with placebo. In addition to 24 patients with probable atypical depression, we studied 46 patients with definite atypical depression in weeks 6 to 12. When these two patient groups are combined, the data clearly support the advantage of a 12-week study.

During the 6- to 12-week period, seven of 17 placebo patients (41%), five of 24 imipramine patients (21%), and two of 30 phenelzine patients (7%) relapsed ($\chi^2=8.2$, df=2, p=0.17). The relapse rate with placebo was greater than that with phenelzine ($\chi^2=6.3$, df=1, p=0.01, one-tailed). Differences between phenelzine and imipramine and between imipramine and placebo were not significant.

The design feature eliminates some transient improvement, resulting in increased power with minimal increase in cost, since major costs occur during screening and workup. It should be considered in planning other antidepressant trials. In addition, since only responders are maintained in the trial, there is no ethical problem with prolonging an ineffective treatment.

DISCUSSION

In these studies, a primary interest has been to test the utility of associated atypical symptoms in identifying patients with reactive mood who selectively benefit from MAOIs. At this time, patient and physician ratings suggest that phenelzine is more effective than imipramine in treating patients with probable atypical depression (those with only one associated symptom). These results (coupled with our previous report of a selective MAOI response with 120 patients with definite atypical depression) suggest that patients who meet the RDC for depressive disorder and who have any of these features and reactive mood selectively benefit from MAOIs.

How much weight should be given to these conclusions? The fact that a total of 180 patients with one or more features has been studied indicates that this is not a fortuitous finding derived from a small patient sample but is robust and generalizable.

The effect size (i.e., the proportion of patients who improved with a drug minus the proportion who improved with placebo) of tricyclic antidepressants is 30%–40% for most patient groups (22). Therefore, since the effect size of tricyclics in patients with atypical depression appears to be closer to 20%, it might be argued that patients with atypical depression are characterized by relatively poor response to tricyclics. Their response rate to MAOIs is the rate expected in a group of depressed patients treated with an effective antidepressant.

The converse of this is that MAOIs should not be effective in the patient group with the best response to tricyclic antidepressants—i.e., patients with melancholia. In order to examine this question, we did two pilot studies of MAOIs in melancholia (23, 24). Unanticipated positive results have encouraged us to initiate a collaborative controlled study of MAOIs in depressed patients with melancholia. MAOIs may have a broad spectrum of activity that includes melancholia as well as reactive and atypical forms of depressive illness. Thus, the widespread clinical belief that the range of efficacy of tricyclics is broader than that of MAOIs may be incorrect.

Although they have been discussed for 20 years, other attempts to identify patients who selectively benefit from MAOIs have been unsuccessful. Including tricyclic-responsive nonmelancholic, anxious, depressed patients in previous studies may have obscured specific effects of MAOIs in patients with associated atypical features. Without prospective randomization, these studies lacked the statistical power to identify a group selectively responsive to MAOIs.

In the group of patients with definite atypical depression, those with a history of panic attacks had a greater differential response to drug and placebo than those without such a history (21). The patients with such a history had a placebo response rate of approximately 10%, whereas those without a history of panic attacks had a placebo response rate of 50%. In contrast, in the patients with probable atypical depression, the placebo response rate was reversed for patients with or without a history of panic attacks. (Those with such a history had a high placebo response rate.) Examination of a variety of variables offered no adequate explanation for this discrepancy. Although a history of panic attacks may have a different significance in patients with definite versus probable atypical depression, a more likely explanation for this discrepancy is sampling fluctuation. That is, some samples of patients with or without a history of panic attacks have a low and others a high rate of placebo response, with the mean of the population of both groups being approximately equal. This explanation is supported by the fact that due to relapse from weeks 6 to 12, the placebo response rate for patients with definite atypical depression and no history of panic attacks dropped to 37% (from 53% at 6 weeks), and the rate for patients with a history of panic attacks dropped to 30% by week 12 (from 60% at week 6). Both groups with high placebo response rates appeared to move toward the mean. We intend to continue to examine this issue in future studies.

Our work also suggests that in a sample of moderately depressed outpatients, many with a chronic course, antidepressants are useful. Many of these patients would previously have been considered to have neurotic or characterologic depression. Differences in antidepressant-placebo outcome suggest that some of their psychopathology may be attributed to a drug-sensitive biological diathesis.

The relatively high response rate with MAOIs, accompanied by the relatively poor response to tricyclic antidepressants, suggests that atypical depression may be a clinically and heuristically useful subtype of depressive illness. The clinician should be cognizant of this symptom complex in treatment prescription, and the investigator should take note of it when studying the biological and genetic basis of unipolar disorder. We think it unfortunate that *DSM-III-R* has not accepted this category, given its historical roots, psychopharmacological validation, and clinical utility.

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Clorazepate and Lorazepam: Clinical Improvement and Rebound Anxiety

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Sixty-two anxious patients were treated under double-blind conditions for 4 weeks with either clorazepate or lorazepam. Two-thirds of each treatment group were then switched abruptly to placebo for 2 weeks, while one-third continued to receive active medication. Two major findings were obtained. About 70% of the patients maintained improvement during the 2-week placebo period. Some patients, however, experienced rebound anxiety, which appeared to be more intense and occurred earlier when placebo was substituted for a benzodiazepine with a short half-life (lorazepam) than for one with a long half-life (clorazepate). The clinical relevance of these findings is discussed.

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The clinical efficacy of benzodiazepines for the treatment of generalized anxiety disorder has been well-established (1, 2). In fact, most improvement occurs during the first week of treatment (3). Although the question of rebound insomnia has been studied extensively (4), rebound anxiety after abrupt discontinuation of benzodiazepine therapy has been thought to occur primarily with therapeutic doses only after prolonged treatment. For example, in a study by Rickels et al. (5), 43% of patients experienced clear withdrawal symptoms and 14% experienced rebound anxiety when treated with benzodiazepines for 1 year or more, but only 5% and 4%, respectively, experienced such symptoms when treated for shorter periods of time. Patients were evaluated, however, only 2–4 weeks after abrupt switch from diazepam to placebo, and more frequent evaluations might well have revealed a higher incidence of rebound anxiety than was reported at that time. In addition, less intense rebound anxiety will probably occur after abrupt discontinuation of long half-life than of short half-life benzodiazepines (6).

Rebound anxiety is identified by a marked temporary return of original anxiety symptoms lasting usually only a few days, while withdrawal symptoms are identified by the presence of marked distress, including original as well as new symptoms, and by a time course indicating symptom appearance after 2–3 days, a peak after 5–7 days, and a slow decrease of symptoms over 2–3 weeks (5). In contrast, recrudescence of original anxiety occurs gradually over a 1–4-week period, and symptom levels are not more marked than before treatment, no new symptoms are present, and usually symptoms do not return to baseline levels without additional treatment. In fact, several clinical studies have indicated that the time at onset and the severity of recrudescence of anxiety after abrupt treatment discontinuation may vary among benzodiazepine anxiolytics as a function of plasma half-life (7, 8).

The present study was therefore designed to compare the clinical efficacy of a long half-life and a short-to-intermediate half-life benzodiazepine over a 4-week treatment period and to determine time at onset and severity of rebound anxiety and of recrudescence of original symptoms should they occur. We hypothesized that recrudescence of original symptoms would extend during the 2-week posttreatment placebo period and that rebound anxiety would represent a more temporary phenomenon.

METHOD

Sixty-two outpatients diagnosed according to *DSM-III* criteria as suffering from generalized anxiety disorder were assigned under double-blind conditions and after a 1-week single-blind placebo washout period to 4 weeks of treatment with either clorazepate (N=32) (15–30 mg/day) or lorazepam (N=30) (2–4 mg/day). Medications were prescribed to be taken in the morning and at bedtime. Patients started with three capsules per day (one in the morning and two at bedtime) during the first week, and the daily dose was raised to four capsules per day for the remaining 3 weeks of therapy. Those patients experiencing disturbing side

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TABLE 1. Adverse Drug Effects in Patients With Generalized Anxiety Disorder Receiving Clorazepate or Lorazepam

	Clorazepate					Lorazepam				
		Patients With Adverse Effects		Dose (mg/day)			Patients With Adverse Effects		Dose (mg/day)	
Week of Treatment	N	N	%	Mean	SD	N	N	%	Mean	SD
1	32	5	15.6	22.5	1.3	30	13	43.3[a]	2.7	0.4
2	31	8	25.8	25.0	3.5	28	7	25.0	3.4	0.6
3	31	7	22.6	25.0	3.9	28	6	21.4	3.4	0.7
4	31	6	19.4	25.0	4.0	27	1	3.7	3.4	0.6

[a] Significantly more patients taking lorazepam than those taking clorazepate reported side effects after 1 week of treatment ($\chi^2=4.5$), df=1, $p<0.05$).

effects were instructed to lower their medication intake but to no fewer than two capsules per day.

After 4 weeks of receiving active medication under double-blind conditions, two-thirds of the active drug patients were switched to placebo for 2 weeks while one-third continued with their original benzodiazepine to maintain the double-blind. Each patient was evaluated by his or her physician daily for the first 3 days of the posttreatment phase and again after days 7 and 14. Patients were informed about the nature of the study and that some of them would be withdrawn from their medication during the last 2 weeks of the study. A signed written informed consent was obtained, and the protocol was approved by the local institutional review board.

All anxious patients considered for this study had to fulfill the following intake criteria both before and after the placebo washout period: a Hamilton Rating Scale for Anxiety (9) total score of 18 or higher, a Covi Anxiety Scale (10) score of 8 or higher, and a Raskin Depression Scale (11) score of 7 or lower. Patients had to be in good physical health and without substantial medical illness that might interfere with the study.

Patients were excluded from the study if they suffered from organic brain syndrome or affective or psychotic disorders, had a history of convulsive disorders, had experienced hypersensitivity to benzodiazepines, or had a history of alcohol or drug abuse. Regular use of benzodiazepines or other psychotropic drugs within 1 month before the study began was also an exclusion criterion, which assured that no benzodiazepine-dependent individual entered the program. Women of childbearing potential had to practice medically acceptable birth control methods. Of the 62 patients who entered the double-blind part of the program, 38 (61%) were women and 42 (68%) were 40 years old or younger. The mean±SD age was 36±10 years for clorazepate patients and 40±11 years for lorazepam patients, a nonsignificant difference.

All the patients in this study were assessed weekly during the 4-week treatment period and more frequently during the 2-week posttreatment phase. The Hamilton anxiety scale total score, the tension-anxiety factor of the Profile of Mood States (POMS) (12), and a 7-point global assessment of improvement (13) were used as measurements to determine outcome.

Before or at least 4 hours after the morning dose of benzodiazepines, 10 cc of blood were drawn for plasma level determinations. Patients were asked to eat a light breakfast. Blood was drawn into a heparinized tube and centrifuged within 1 hour after venipuncture. The plasma portion was then immediately transferred to a clean tube that was labeled, capped, taped tightly closed, and immediately frozen at −4° C or lower. Labels were provided that included the patient's name, the date blood was drawn, and the time of sampling. All samples were collected and mailed to one of us (D.J.G.) for drug plasma level determinations. Plasma concentrations of desmethyldiazepam in clorazepate-treated patients or of lorazepam in lorazepam-treated patients were determined by electron-capture gas-liquid chromatography (14, 15).

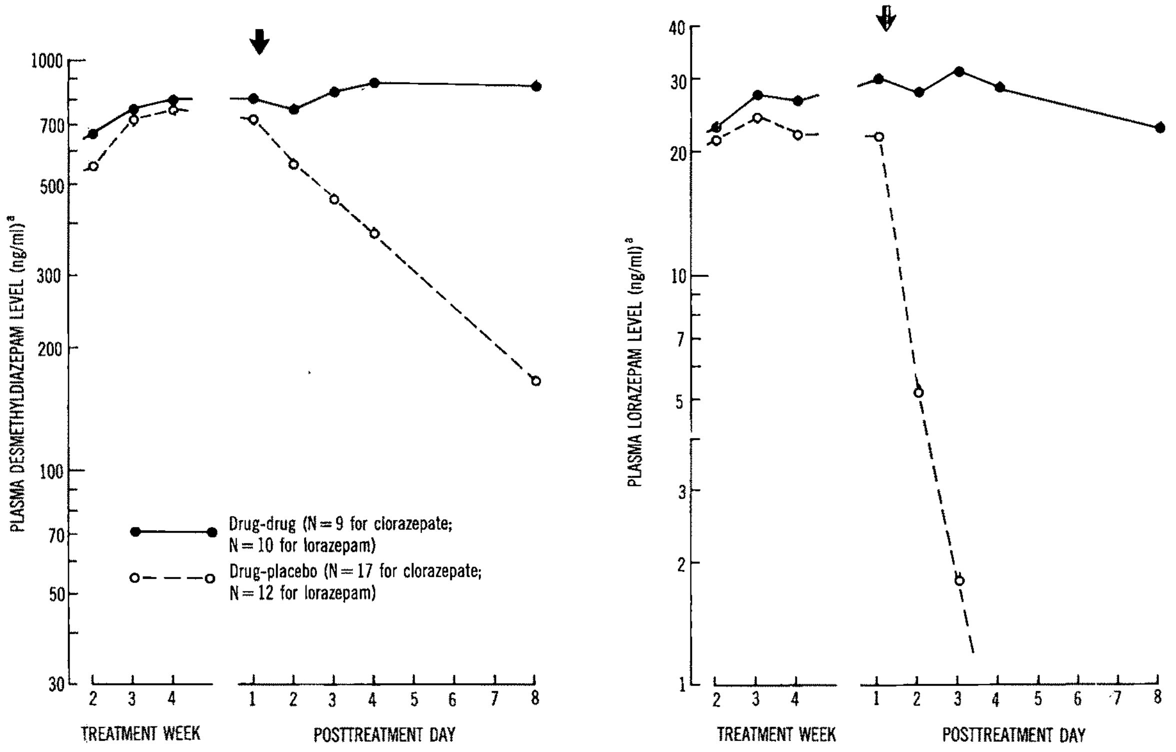
Treatment groups were compared initially to demonstrate that randomization produced treatment groups similar in psychopathology, illness history, and demography. To evaluate clinical improvement as well as return of symptoms, analysis of variance (ANOVA) was used for global improvement and analysis of covariance (ANCOVA) for Hamilton anxiety scale and POMS tension-anxiety posttreatment scores. Baseline scores were used as covariates for the assessments at weeks 1, 2, 3, and 4 of the treatment phase, and 4-week scores were used as covariates for the assessments of the 2-week posttreatment period. The number of patients reporting side effects from each drug was compared by chi-square analysis. All significant findings are conservatively expressed as two-tailed.

RESULTS

Neither physical examination, laboratory tests (CBC, SMA-12, and urinalysis), nor vital signs (blood pressure, pulse) showed any significant change as a function of either drug or study duration. Initial urine drug screens were conducted after the placebo washout period and were negative for phenothiazines, amphetamines, barbiturates, opiates, methaqualone, and benzodiazepines.

The number of patients reporting side effects and the mean daily medication dose for each evaluation period are given in table 1. Sedation was the only major side

FIGURE 1. Clorazepate and Lorazepam Plasma Levels for Patients With Generalized Anxiety Disorder Who Continued to Receive Active Drug or Were Abruptly Switched to Placebo



aLogarithmic scale.

TABLE 2. Clinical Improvement[a] for Patients With Generalized Anxiety Disorder Receiving Clorazepate or Lorazepam

	Baseline Score (N=62)		Week 1 Score				Week 2 Score				Week 4 Score			
			Clorazepate (N=32)		Lorazepam (N=30)		Clorazepate (N=31)		Lorazepam (N=28)		Clorazepate (N=31)		Lorazepam (N=27)	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hamilton anxiety	27.3	7.5	18.5	6.5	20.0	9.6	13.5	7.8	14.4	6.7	9.5	3.9	8.6	4.4
POMS tension-anxiety	22.5	8.1	17.4	8.3	19.8	9.7	15.5	6.8	16.1	8.7	13.7	7.5	12.5	9.0
Global improvement			3.1	1.0	3.7	1.2	2.9	1.0	3.4	1.2	3.1	1.1	3.1	1.1

[a] Mean±SD treatment scores were covariance adjusted for baseline scores. Covariance analyses indicated no significant differences between treatment groups. Both treatment groups were already significantly improved from baseline at week 1 on all three improvement measures ($t=3.4–9.1$, $df=61$, $p<0.01$).

effect, occasionally necessitating adjustment of dose. Only during the first week of treatment did significantly more patients taking 2.7 mg/day of lorazepam report side effects than patients taking 22.5 mg/day of clorazepate. The reverse was true after 4 weeks of treatment, but this reversal did not reach statistical significance. Pill counts, physician inquiry into dose intake, and plasma level determinations assured excellent treatment compliance.

Plasma levels of desmethyldiazepam and of lorazepam are given in figure 1. The mean ± SD postdose washout half-lives were calculated to be 73.2 ± 4.2 hours for clorazepate and 13.9 ± 2.2 hours for lorazepam. Figure 1 clearly indicates that the desmethyldiazepam disappeared slowly from the plasma and the lorazepam disappeared rather swiftly after discontinuation of treatment. Among patients who continued receiving active drug treatment, plasma concentrations remained similar to the values obtained during the first 4 weeks of treatment.

The data presented in table 2 indicate that both benzodiazepines produced a significant symptom decrease over time and did not differ with respect to improvement rate. The dropout rate was rather low (one clorazepate patient and three lorazepam patients). The baseline (prestudy) scores (table 2) clearly indicate that patients fulfilled our intake criteria.

When patients were shifted for 2 weeks to placebo,

TABLE 3. Adjusted Posttreatment Scores[a] on Three Outcome Measures for Patients With Generalized Anxiety Disorder Who Continued to Receive Benzodiazepines or Were Abruptly Switched to Placebo

	Clorazepate Group							Lorazepam Group							
	Active Drug			Switched to Placebo				Active Drug			Switched to Placebo				
		Score			Score				Score			Score			
Measure	N	Mean	SD	N	Mean	SD	Newman-Keuls Test	N	Mean	SD	N	Mean	SD	Newman-Keuls Test	F
Posttreatment day 3															
Hamilton anxiety	10	6.7	3.5	18	9.6	5.8	n.s.	10	7.3	3.1	16	12.0	6.1	p<0.10	2.26[b]
POMS tension-anxiety[c]	10	8.8	3.6	18	13.7	9.2	n.s.	10	8.5	3.7	16	19.3	12.7	p<0.01	4.97[d]
Global improvement[e]	10	2.4	0.9	18	3.5	1.2	n.s.	10	2.9	1.2	16	4.3	1.2	p<0.05	4.76[d]
Posttreatment day 7															
Hamilton anxiety	10	5.5	4.1	18	10.9	7.4	p<0.05	10	8.2	2.7	12	9.3	3.9	n.s.	2.70[f]
POMS tension-anxiety	10	7.3	3.9	18	14.4	7.1	p<0.05	10	12.5	8.7	12	12.2	6.9	n.s.	3.19[g]
Global improvement	10	2.6	1.0	18	3.4	1.4	n.s.	10	2.9	1.3	12	4.1	1.5	p<0.10	3.01[g]

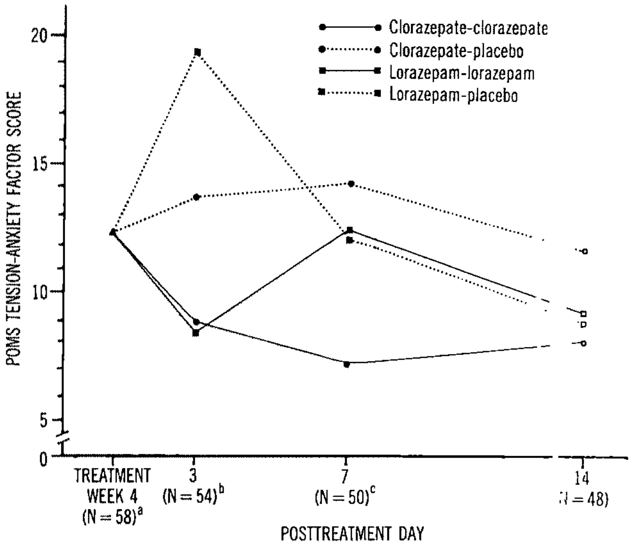
[a] Mean±SD scores were covariance adjusted for 4-week scores obtained at the end of the treatment phase.
[b] df=3,51, p<0.10.
[c] Significant difference between the clorazepate-placebo and the lorazepam-placebo groups (Newman-Keuls, p<0.05).
[d] df=3,51, p<0.01.
[e] Nonsignificant difference between the clorazepate-placebo and the lorazepam-placebo groups (Newman-Keuls, p<0.10).
[f] df=3,47, p<0.10.
[g] df=3,47, p<0.05.

13 (72.2%) of the 18 clorazepate-placebo patients and 12 (75%) of the 16 lorazepam-placebo patients maintained the clinical improvement levels obtained after 4 weeks of active drug therapy, including five clorazepate-placebo and two lorazepam-placebo patients who experienced temporary rebound anxiety.

Table 3 gives mean ± SD scores for the three primary outcome measures obtained at days 3 and 7 of the posttreatment phase. Clearly, anxiety increased at day 3 for both benzodiazepine groups who were shifted to placebo; lorazepam patients experienced the most marked anxiety increase. After 7 days, the rating scale scores of the patients who were shifted from lorazepam to placebo reflected the anxiety levels of these patients before placebo substitution, and differences between patients maintained on clorazepate and those shifted to placebo reached significance. Day 7 data reflect the fact that four lorazepam-placebo patients dropped out on or after day 3 and were therefore excluded from day 7 analyses.

We chose the results obtained with the POMS tension-anxiety factor as representative of our outcome results. Figure 2 indicates a significantly higher symptom increase at day 3 for lorazepam-placebo patients than for clorazepate-placebo patients, a difference that disappeared at day 7. However, at day 7 a significant difference was present between patients maintained on clorazepate and those shifted from clorazepate to placebo; this difference appears to be contributed to by patients who continued to improve on clorazepate in the first week of the posttreatment phase and by patients whose scores slightly worsened while receiving placebo. No significant treatment group differences were observed at day 14. Data interpretation is conservative, since the scores for dropouts who experienced substantial anxiety increases were not carried forward to days 7 and 14.

FIGURE 2. Mean POMS Tension-Anxiety Scores at Posttreatment Days 3, 7, and 14 for Patients With Generalized Anxiety Disorder Who Continued to Receive Active Drug or Were Abruptly Switched to Placebo



[a] Covariance-adjusted mean score.
[b] Significant difference (Newman-Keuls) between the lorazepam-lorazepam group and the lorazepam-placebo group (p<0.01) and between the clorazepate-placebo group and the lorazepam-placebo group (p<0.05); nonsignificant difference between the clorazepate-clorazepate group and the clorazepate-placebo group (p<0.20).
[c] Significant difference (Newman-Keuls) between the clorazepate-clorazepate group and the clorazepate-placebo group (p<0.05).

Using a Hamilton anxiety scale score increase of 5 or more occurring during the first week of placebo substitution as an indicator of rebound anxiety, we found that five (31%) of 16 lorazepam-placebo patients and five (28%) of 18 clorazepate-placebo patients experienced rebound anxiety at day 3, as did one (6%) of 16 lorazepam-placebo patients and three (17%) of 18 clorazepate-placebo patients at day 7. Four lorazepam-placebo patients dropped out after day 3 and two clorazepate-placebo patients dropped out after day 7 because of severe rebound anxiety. The mean ± SD Hamilton anxiety score increases for patients experiencing rebound anxiety during the first week of placebo were 14.2 ± 11.6 for lorazepam-placebo and 10.1 ± 6.9 for clorazepate-placebo patients.

DISCUSSION

Our data indicate that temporary rebound anxiety may occur in selected anxious patients when short-term (4 weeks) benzodiazepine therapy is abruptly discontinued. Using a temporary increase of 5 points or more on the Hamilton anxiety scale as an indication of a rebound phenomenon, we found that 37% of the patients switched from lorazepam to placebo and 45% of those switched from clorazepate to placebo experienced such rebound. A stricter criterion of rebound anxiety (namely, a Hamilton anxiety score increase to at least prestudy levels) classified only 25% of the patients switched from lorazepam to placebo and 17% of the patients switched from clorazepate to placebo as experiencing rebound anxiety.

Clearly, rebound anxiety does not occur in every anxious patient after a short course of benzodiazepine therapy; however, if it does occur, intensity and time course appear to be related to drug plasma half-life, since lorazepam-placebo patients experienced rebound anxiety more intensely and earlier than clorazepate-placebo patients. One may speculate that temporary rebound anxiety may be a reflection of the altered nature of the benzodiazepine receptors, which may have increased in number or have otherwise become more sensitive with chronic benzodiazepine therapy (16).

A surprising finding was that about 70% of all the anxious patients who were switched to placebo maintained improvement over the 2-week double-blind postbenzodiazepine treatment period. Conservatively, we counted dropouts as not maintaining improvement. These results are similar to a previous finding (5) that 50% of chronic anxious patients treated for 6 weeks with diazepam maintained improvement after being switched to placebo for at least 4 weeks.

Since the present study was conducted, several reports (17–20) have been published of "severe withdrawal symptoms" or "severe rebound anxiety" occurring after only 4–6 weeks of benzodiazepine therapy; however, the data reported can be interpreted to indicate a return of original anxiety symptoms rather than a rebound anxiety syndrome (21). Since the patients in these studies were evaluated only weekly or biweekly after benzodiazepine discontinuation, it is unlikely that transient rebound phenomena would have been detected even if they existed.

Although we believe that our methodology was most appropriate for assessing degree and intensity of rebound anxiety and for separating such rebound anxiety from a recurrence of original anxiety symptoms, there were some patients (four lorazepam-placebo and two clorazepate-placebo patients) who dropped out because of severe rebound anxiety; while these patients clearly fulfilled the definition of rebound anxiety, it is impossible to know with any degree of certainty whether or not any of these dropouts would also have experienced a return of original symptoms. For those patients who continued to receive placebo for the full 2 weeks, the determination of rebound anxiety as a function of plasma half-life could, however, clearly be established.

Our results appear to have clinical relevance. A significant number of anxious patients responded well to short-term benzodiazepine therapy and maintained improvement for at least 2 weeks after being shifted to placebo. Yet, a subgroup of patients experienced rebound anxiety after only 4 weeks of benzodiazepine therapy; their symptoms were slightly more intense and occurred earlier after treatment discontinuation with short half-life than long half-life benzodiazepines. A similar observation was made when patients with insomnia were treated with benzodiazepines (4–6).

Good medical practice should therefore include a period of tapering even after short-term benzodiazepine therapy. Our finding clearly supports short-term benzodiazepine use for the management of patients with generalized anxiety disorder and warns physicians not to interpret mistakenly a substantial return of symptoms that occurs early after benzodiazepine discontinuation as a recurrence of original symptoms necessitating further therapy. Such guidelines are important for clinical practice because the few patients who experience rebound anxiety after only 4 weeks of benzodiazepine therapy and who resume benzodiazepine therapy needlessly may represent the very patients who become chronic users of benzodiazepines.

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HPA Axis Abnormalities in Depressed Patients With Normal Response to the DST

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In order to identify depressed patients with hypothalamic-pituitary-adrenal (HPA) axis abnormalities who have a normal response to the dexamethasone suppression test (DST), the authors administered a series of neuroendocrine tests including insulin-induced hypoglycemia, arginine vasopressin challenge, and a DST. Using standard sensitivity measures, as well as logistic regression, they concluded that many patients with HPA abnormalities are not identified by the DST. These findings suggest that other neuroendocrine tests, which are sensitive to HPA axis abnormalities, may be helpful in subtyping depression on the basis of HPA axis functioning.

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During the past decade the most popular biological marker of depression has been failure of cortisol suppression after a standard dexamethasone suppression test (DST). The sensitivity of the DST is relatively low; however, its specificity, although somewhat controversial, is encouraging and allows the test to be useful in the research of depressive disorders (1). To develop more sensitive biological strategies for identifying and investigating depression, many investigators have used a series of "biological marker" tests. These have often included sleep EEG (2, 3), thyrotropin-releasing hormone (TRH) (4, 5), or other hormonal tests (6) combined with the DST. In many of these investigations, postdexamethasone cortisol levels may represent the only indication of hypothalamic-pituitary-adrenal (HPA) axis abnormality. Even in investigations of single specific biologic markers, the DST status of experimental subjects is often included as an indicator of HPA axis function (7, 8). Furthermore, many investigators have included DST status in various schemata for subtyping depression, inferring differential pathophysiology (9, 10). Obviously, much significance is attached to DST status and reasons for its poor sensitivity become important.

There are many reasons for poor sensitivity in any diagnostic tool, but in this situation two basic considerations seem to be particularly important. One possible hypothesis would suggest that the DST is an excellent marker of HPA axis abnormality, but few depressed patients have abnormalities in this system. Alternatively, the DST may be a poor way to identify HPA abnormalities, which may actually be quite common in patients with depression. Their distinction becomes important, especially when the DST is used to subtype depression. In the first hypothesis, patients would be neatly categorized into one subtype of depression with HPA abnormalities and one without HPA abnormalities. Pathophysiologic differences between such groups could easily be inferred. In the latter hypothesis, pathophysiologic differences would be obscured and a variety of other variables, including severity, number of episodes, and age, would require consideration.

Recently, investigators have begun to use other techniques to evaluate the HPA axis in depressed patients, and patients with HPA abnormalities are being found who have not been identified by the DST (11). We are currently using a series of neuroendocrine tests that includes arginine vasopressin challenge and insulin-induced hypoglycemia, as well as dexamethasone suppression, to investigate the HPA axis in depression. Arginine vasopressin reliably stimulates cortisol secretion (12). Specific arginine vasopressin receptors have been identified on the anterior pituitary corticotroph cell (13), and its effect on the HPA axis is mediated by ACTH release (14). Patients with depression demonstrate a significantly greater cortisol response to arginine vasopressin stimulation than do normal control subjects (7). This hypersecretory response of cortisol may be a function of adrenal hypersensitivity to ACTH rather than a function of increased ACTH secretion, since ACTH levels do not differ between depressed patients and control subjects (7). Regardless, the differential cortisol response and similar ACTH response after injection of arginine vasopressin represent the rationale for our use of

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cortisol levels after arginine vasopressin injection rather than ACTH as the marker in this test.

Insulin-induced hypoglycemia, on the other hand, is associated with differential ACTH response. Depressed patients display blunted ACTH levels after insulin-induced hypoglycemia when compared to control subjects (8). Insulin-induced hypoglycemia apparently acts centrally and is mediated through hypothalamic glucose receptors (15). Depressed patients may show blunted ACTH release after insulin-induced hypoglycemia while at the same time demonstrating functional adrenal hyperplasia and adrenal hypersensitivity to ACTH (8). Therefore, a subject who demonstrates blunted ACTH response may show a normal postinsulin cortisol level. For this reason, ACTH is chosen as the marker in the insulin-induced hypoglycemia test.

Using a strategy that included all three tests on every subject, this study investigated the frequency of HPA axis abnormalities despite normal cortisol response to dexamethasone. On the basis of our findings, we discuss alternative neuroendocrine tests or combinations of neuroendocrine tests that might increase the ability to detect HPA axis dysfunction.

METHOD

Subjects

Twenty-three patients, 16 women and seven men, were recruited from the inpatient service of the University of Iowa psychiatric department. The mean±SD age of the patient population was 31.1±9.6 years, with a range of 21–58 years. All met *DSM-III* criteria for a major depression, and diagnoses were confirmed by the NIMH Diagnostic Interview Schedule (DIS) (16). The mean±SD Carroll score (17) of the depressed patients was 30.2±9.2. Control subjects were recruited through an advertisement in the local newspaper. They were screened with the DIS and were excluded if an axis I diagnosis or antisocial personality disorder was identified. The final control sample consisted of 19 subjects, 10 men and nine women. The mean±SD Carroll score of the control subjects was 1.7±1.3. Thus, our total sample consisted of 42 subjects, 23 depressed patients and 19 control subjects. All analyses deal with this group. The total sample consists of the subset of subjects who were included in the studies by both Lopez et al. (8) and Meller et al. (7), along with a smaller number of subjects who also met inclusion criteria and had been given all three tests but had not been included in earlier reports.

Procedure

Informed consent was obtained; medical and endocrine histories were obtained; and physical examination, CBC, serum electrolytes and blood chemistry screen, thyroid screen, and an ECG were performed on all subjects. Subjects who displayed evidence of significant medical problems, substance abuse, or current use of drugs known to interfere with HPA axis functioning were excluded (18). Medication regimens prescribed by ward physicians were unaltered. Some patients were being treated with various antidepressants, lithium, neuroleptics, or a combination of medications.

On the first day of testing all subjects received 0.18 pressor units/kg of body weight of arginine vasopressin intramuscularly at 4:00 p.m. The butterfly catheter was placed at least 30 minutes before blood samplings. Blood was drawn immediately before injection and at 15, 30, 45, 60, and 90 minutes after injection. Samples were prepared as described by Meller et al. (7).

After 24 hours had elapsed, all subjects received regular purified pork insulin at a dose of 0.15 units/kg of body weight by means of an intravenous bolus at 4:00 p.m. The catheter was again placed at least 30 minutes before blood sampling. Blood samples were obtained immediately before injection and at 15, 30, 45, 60, and 90 minutes after injection. Samples were prepared as described by Lopez et al. (8). Subjects who did not reach a glucose nadir of less than 40 mg/dl, a level that has been shown to be a reliable stimulator of the HPA axis, were excluded from our study (8).

Twenty-four hours after insulin testing, all subjects received a standard DST consisting of 1 mg of dexamethasone given orally at 11:00 p.m., and plasma cortisol levels were assessed at 8:00 a.m. and 4:00 p.m. the following day. Nonsuppression was defined as postdexamethasone cortisol levels of more than 5.0 μg/dl.

The University of Iowa Medical Research Facility laboratory has developed and validated its own radioimmunoassay for ACTH and cortisol. A specific description of these procedures can be found in Pfohl et al. (19).

The issue of defining normal and abnormal neuroendocrine response to arginine vasopressin challenge and insulin-induced hypoglycemia must be addressed. Because few studies employing these methods have been carried out, there are no generally accepted definitions. Given the preliminary nature of this study, a conservative and traditional statistical technique for defining abnormality is most appropriate. Since cortisol response after arginine vasopressin challenge follows a normal distribution and is significantly increased in depressed patients (7), cortisol hyperresponse after arginine vasopressin challenge will be defined as a Δ_{max} cortisol level that is more than two standard deviations from the mean Δ_{max} response of the control population. The cutoff value was determined to be 13.0 μg/dl.

ACTH secretion after insulin-induced hypoglycemia, however, is blunted in major depression (8), and because of its pulsatile secretion and short half-life (20), ACTH response is not normally distributed. In order to approximate normal distribution, Δ_{max} ACTH must be log transformed (after the addition of

TABLE 1. Prediction of Depression by Four Neuroendocrine Test Models in 23 Patients With Major Depression

Model	Overall Goodness of Fit			Improvement Over DST Alone			Beta Coefficients for Each Predictor					
							DST		Arginine Vasopressin Challenge		Insulin-Induced Hypoglycemia Challenge	
	Likelihood Ratio (χ^2)	df	p	Likelihood Ratio (χ^2)	df	p	Beta	SE	Beta	SE	Beta	SE
DST alone	3.61	1	0.0575				1.85[a]	1.13				
DST+arginine vasopressin challenge	8.36	2	0.0153	4.75	1	0.0293	2.15	1.17	0.17[b]	0.08		
DST+(log) insulin-induced hypoglycemia challenge	13.08	2	0.0014	9.47	1	0.0021	1.36	1.21			−0.89[b]	0.38
DST+arginine vasopressin challenge+(log) insulin-induced hypoglycemia challenge	14.97	3	0.0018	11.36	2	0.0034	1.30	1.21	0.12	0.09	−0.81[b]	0.38

[a] $p<0.06$.
[b] $p<0.05$.

1 to adjust for zeroes). The mean and standard deviation of the logs of the Δ_{max} ACTH data were computed. An abnormal ACTH response was defined as one that, when transformed to the log scale, was at least two standard deviations below the mean of the log Δ_{max} ACTH of the control population. The cutoff Δ_{max} ACTH value thus determined was 11.1 pg/ml.

Statistical Analysis

Post-arginine vasopressin Δ_{max} cortisol levels and post-insulin Δ_{max} ACTH levels were compared for depressed patients and control subjects with the Student's t test. The ACTH values were log transformed. If variances differed significantly between control and depressed patients by the standard F test, the adjusted t test for unequal variances with adjusted degrees of freedom was used. Sensitivity and specificity values were calculated by using standard equations (21).

Logistic regression was used to assess the ability of arginine vasopressin and/or insulin-induced hypoglycemia to improve the detection of depression as compared to the DST alone. Logistic regression models the log odds of a binary outcome variable (depressed or control) as a function of several predictor variables (the DST, arginine vasopressin, and insulin-induced hypoglycemia test scores) (22, 23). The design of this study was separate sampling. A sample of depressed patients was obtained and their scores on the DST, arginine vasopressin test, and insulin-induced hypoglycemia test were measured; a similar procedure was used for control subjects. Logistic regression is appropriate for this study design (24).

Four different logistic models were applied to the data by using the Statistical Analysis System procedure PROC LOGIST (23). The baseline model used just the DST. The other three models added the two other tests in various combinations. Thus, the four models were the DST alone; the DST and arginine vasopressin; the DST and insulin-induced hypoglycemia; and the DST, arginine vasopressin, and insulin-induced hypoglycemia. All models included the DST, which was treated as a binary variable with abnormal coded as 1 and normal coded as 0. The two other predictors, arginine vasopressin and insulin-induced hypoglycemia, were not coded; the actual Δ_{max} values were used because of the potentially greater power and practical usefulness. The values for insulin-induced hypoglycemia were log transformed, as described earlier. (Alternative analyses that coded them as normal or abnormal led to the same conclusion.)

The results of doing a logistic regression can be summarized in two ways, both of which are included. The first (table 1) gives global summary goodness of fit statistics for each model fit to the data. The likelihood ratio statistic shows how much better a given model fits the data than a null model, which has no predictors and assumes that all patients have an equal likelihood of depression. It can also be used to compare two different models—a simple model and a more complex model with additional predictor variables. The difference between the likelihood ratio statistics tells whether the additional predictor variables make a significant contribution. The likelihood ratio statistic is distributed as a chi-square statistic with degrees of freedom determined by the number of variables fit into the model.

The second way of summarizing the logistic regression analysis (table 1) is to give the details for each model considered—the beta coefficients for each predictor in the model, the standard errors, and the p values. The beta coefficient for a predictor variable tells how much that predictor increases the log odds of the outcome, all other things being equal. Exponentiating the beta coefficient gives the odds ratio due to that factor. For example, consider a model using the DST and insulin-induced hypoglycemia to predict depression. Logistic regression gives one a beta coefficient estimate for the DST, β_{DST}, and another for insulin-induced hypoglycemia (IH), β_{IH}. The quantity exponent (β_{DST}) measures how much an abnormal score on the DST increases the odds of depression as

FIGURE 1. Mean±SD Δ_{max} Cortisol Levels for 23 Patients With Major Depression and 19 Control Subjects After Arginine Vasopressin Challenge

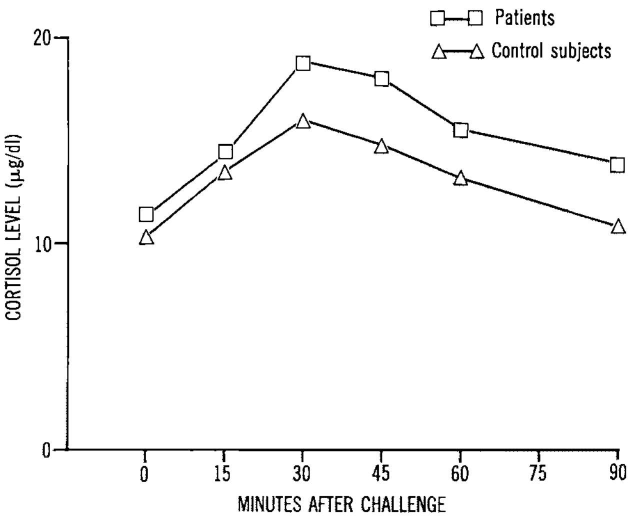

FIGURE 2. Mean±SD Δ_{max} ACTH Levels for 23 Patients With Major Depression and 19 Control Subjects After Insulin-Induced Hypoglycemia Challenge

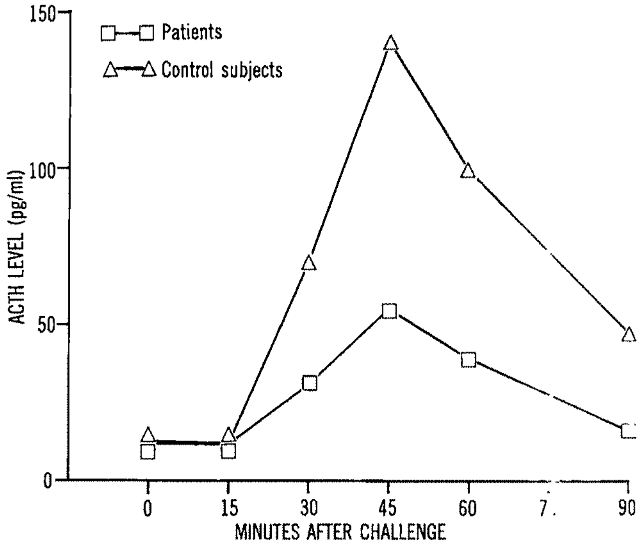

TABLE 2. Sensitivity and Specificity of Neuroendocrine Tests Given to 23 Patients With Major Depression

Test	Sensitivity (%)	Specificity (%)
DST	26	95
Arginine vasopressin challenge	26	100
Insulin hypoglycemia challenge	30	95
DST+arginine vasopressin challenge	48	89
DST+insulin hypoglycemia challenge	43	95
Arginine vasopressin challenge+insulin hypoglycemia challenge	48	95
DST+arginine vasopressin challenge+insulin hypoglycemia challenge	57	89

compared to a normal score, when the score on insulin-induced hypoglycemia is held constant. The quantity exponent (β_{IH}) tells how much the odds of having depression increase for each unit decrease in ACTH levels after insulin-induced hypoglycemia, when DST is held constant.

RESULTS

Six of 23 depressed patients (26%) were nonsuppressors on the DST, and one of 19 control subjects (5%) was a nonsuppressor. Given this sample, the DST had a sensitivity of only 26% and a specificity of 95%.

Mean±SD Δ_{max} cortisol levels after arginine vasopressin challenge were significantly greater for the depressed patients (9.1±5.3 µg/dl) than for the control subjects (6.4±3.3 µg/dl) ($t=-2.0$, $df=37.7$, $p=0.05$) (figure 1). Six depressed patients and no control subjects were defined as abnormal on the basis of the above criteria. Thus, the sensitivity of the arginine vasopressin test was identical to that of the DST, and the specificity was 100% in this population. It should be noted, however, that these two tests identified different patients as "abnormal," with only one patient being abnormal on both tests.

The time course of ACTH levels after insulin-induced hypoglycemia are shown in figure 2. The mean±SD Δ_{max} ACTH level for the depressed population was 46.1±43.2 pg/ml and for the control subjects it was 135.1±97.4 pg/ml. The two groups were compared statistically in the log scale, and the depressed patients had significantly smaller log Δ_{max} ACTH levels than the control subjects (3.09±1.63 and 4.55±1.03, respectively; $t=3.5$, $df=37.6$, $p<0.01$). Seven depressed patients and one control subject had an abnormally blunted ACTH response, giving the insulin-induced hypoglycemia test a sensitivity of 30% and a specificity of 95% in this sample.

The three separate tests identified different subsets of patients as "abnormal," with no subject being abnormal on all three tests. Six depressed patients (26%) were abnormal on two of three tests, while no control subjects were identified as abnormal on more than one test. Thirteen of the depressed patients (57%) and two of the control subjects (11%) were identified as abnormal on at least one test. Of the 13 depressed patients, only six were identified by the DST.

Because two of the three tests identified a different control subject as abnormal, combining tests may decrease specificity, but since the tests also identified different depressed patients as abnormal, their combination increases sensitivity, as shown in table 2.

Table 1 summarizes the results of four different logistic regression models applied to the data. It presents the overall summary statistics of the four models, emphasizing goodness of fit measures, and gives the beta coefficients and standard errors. One can see that using the DST alone is of borderline significance. Adding either arginine vasopressin or insulin-induced hypoglycemia challenge significantly and substantially improves the fit. In fact, the addition of either test means that the DST is no longer of even borderline significance (table 1).

Finally, adding both arginine vasopressin and insulin-induced hypoglycemia to the model increases the number of depressed patients identified as abnormal and increases the likelihood ratio chi-square statistic. Note that with the addition of the insulin-induced hypoglycemia challenge, neither the DST nor the arginine vasopressin test is a significant predictor. Insulin-induced hypoglycemia is more sensitive, with equal or greater specificity, and overshadows the other two tests in this model. Therefore, the logistic regression model shows that arginine vasopressin and especially insulin-induced hypoglycemia are more powerful predictors of depression than the standard DST in this small sample.

DISCUSSION

Of the 23 patients who satisfied *DSM-III* criteria for major depression, we identified seven patients with HPA axis abnormalities who responded normally to a standard DST. In fact, the DST failed to identify the majority of patients with HPA abnormalities in this population. It would seem, then, that the poor sensitivity of the DST stems at least in part from its inability to identify many patients who do have HPA abnormalities. It is very likely that some patients with major depression do not have HPA axis dysfunction (10 depressed patients in this study were normal on all three tests), but if such patients are to be categorized into a normal HPA subtype, tests other than the DST are clearly necessary.

It should be noted that the rate of DST nonsuppression in this sample was somewhat lower than the 30%–50% figures often reported in inpatient depressed populations. Rather than reflecting a difference in DST procedure, we feel this low nonsuppression rate reflects two major biases produced by our inclusion/exclusion criteria. First, patients being treated with carbamazepine were excluded from the sample because of carbamazepine's possible interfering effects on the DST (19). This exclusion criterion tended to select out lithium-nonresponsive bipolar patients in the depressed phase, a population in which high rates of nonsuppression would be expected (26). Four such patients were excluded from this study (two nonsuppressors and two who received no DST). Second, patients included in this study had to be able to cooperate with three neuroendocrine tests over a period of several days. Patients suffering from agitated, psychotic illness were therefore less likely to participate, again reducing a population which has been shown to have a high rate of nonsuppression (25).

Although the depressed patients in this study were receiving various psychotropic medications that might alter HPA responsiveness, we do not believe medication effects played a major role in our findings. In previously cited work, patients given arginine vasopressin (7) and insulin-induced hypoglycemia (8) challenges were grouped by psychotropic medications received. When the HPA response was compared between groups, no differences were found. Further, in a study by Wysham et al. (26), control subjects received an arginine vasopressin challenge test before and after a 2-week period of tricyclic antidepressant administration. The tricyclic had no effect on HPA responsiveness. Similarly, Holl et al. (27) performed insulin challenge tests before and after single-dose administration of tricyclics and found no significant differences. Unfortunately, sample sizes have been small, and only tricyclics have been prospectively studied. More work will be necessary to completely determine the effects of psychotropic medications on HPA functioning.

The endocrine challenge tests administered in this study were separated by only 24 hours. Therefore, possible carry-over effects of the previous day's testing are a concern. The half-lives of arginine vasopressin and regular insulin are very short, and little, if any, effects should be present 24 hours later. Nonetheless, tests were scheduled the same for both patients and control subjects, so any carry-over effects were controlled and should not play an important role in between-group comparisons.

In this sample, the arginine vasopressin challenge test was equal to the DST in identifying HPA abnormalities, and the insulin-induced hypoglycemia challenge test was markedly superior (table 1). The combination of any two tests increases the sensitivity with no loss (DST plus insulin-induced hypoglycemia) or only moderate loss (DST plus arginine vasopressin) of specificity. Finally, the use of all three tests serially results in a markedly increased sensitivity (26% for the DST alone, 57% for all three tests), while excellent specificity is retained (95% for the DST alone, 89% for all three tests). It must be kept in mind, however, that although sensitivity and specificity are often used for describing "diagnostic" tools in research populations (8), and numerical values of sensitivity and specificity are illustrative of the "pick up" rate for these three tests in this specific sample, our study in no way addresses the concept of sensitivity and specificity in an epidemiologic sense. No nondepressed psychiatric control subjects were included, and specificity and sensitivity values may be very different in the "real world." An alternative method for evaluating the differential advantages of these three tests uses logistic regression, a standard statistical technique for expressing the probability of a binary outcome variable as a function of a set of predictors that may be qualitative or quantitative (22). Since we are considering both qualitative (DST) and quantitative (arginine vasopressin and insulin) values as independent or predictor variables, logistic regression is particularly well-suited to our use. One obvious advantage to this strategy is its lack of dependence on arbitrarily defined cutoff points necessary for the normal-abnormal distinction required in the sensitivity-specificity analysis. As displayed in table 1, the DST considered alone gives only borderline significance. If either arginine vasopressin or insulin-induced hypoglycemia or both are added, the goodness of fit statistics are significantly improved, implying increased ability to identify patients with HPA axis dysfunction.

It is quite interesting to note that tables 1 and 2 show a tendency for the test that challenges the axis at the level of the hypothalamus, i.e., insulin hypoglycemia, to be more sensitive than the more peripheral tests, i.e., the DST and arginine vasopressin. Insulin-induced hypoglycemia also separates the groups more accurately. Although there was overlap between the control subjects and depressed patients on all three tests, this overlap was considerably smaller on the insulin-induced hypoglycemia as indicated by its greater t statistic (see Results), and it is not surprising that it was a better predictor in the logistic regression. Perhaps the suprahypophyseal abnormalities appear earlier in the course of the disease, or depressive episodes need to be more severe before peripheral abnormalities develop. Future research is necessary to clarify this relationship.

Alternative tests of HPA function could be considered. Exogenous ACTH stimulation has been used to test the HPA axis, and differential adrenal responses between depressed patients and normal control subjects have been reported (28). This technique represents a more direct test of adrenal functioning and may have diagnostic potential.

Recently, corticotropin-releasing hormone (CRH) has become available, and investigators from various research groups have documented differential ACTH response between depressed patients and normal control subjects (29, 30). These investigators have suggested that at least certain forms of depression are associated with chronic CRH hypersecretion. Exogenous CRH challenge may turn out to have important diagnostic implications in the future.

In conclusion, we have demonstrated that the DST is not sensitive to HPA axis abnormalities in some depressed patients and have suggested a possible strategy for improving our ability to identify those patients with HPA abnormalities. Clearly, clinical use of serial neuroendocrine testing is cumbersome and expensive, as well as noxious to the patient and without clinical utility at present. In research protocols, however, particularly those concerned with subtyping depression, more sensitive tests for HPA abnormalities are important. This study represents preliminary research and includes patients who are currently being treated with a variety of medications that may possibly interfere with normal endocrine functioning. Future research should include unmedicated depressed patients as well as a large nondepressed psychiatric control population so that reliable sensitivity and specificity values of these tests in the total population may be better understood. If this were accomplished, serial neuroendocrine test strategies might be helpful in the differential diagnosis of difficult psychiatric presentations such as schizoaffective disorder and schizophreniform disorder.

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The Manfred S. Guttmacher Award

The American Psychiatric Association and the American Academy of Psychiatry and the Law invite applications for the annual Manfred S. Guttmacher Award. The award is given for an outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work presented at any professional meeting or published between May 1, 1987, and April 30, 1988. The award will be formally presented in May 1989 at the American Academy of Psychiatry and the Law meeting held in conjunction with the American Psychiatric Association Annual Meeting in San Francisco, Calif. The recipient is expected to give an award lecture. The award includes an honorarium of $500 and a plaque and will be acknowledged in the APA Convocation program. A nonmember winner's travel expenses will be reimbursed up to $500.

Anyone wishing to apply should submit six copies of the work, along with six copies of an abstract, to Robert L. Stubblefield, M.D., Chairman, Guttmacher Award Board, American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005.

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Insulin Resistance After Oral Glucose Tolerance Testing in Patients With Major Depression

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An association between affective disorders and alterations in glucose utilization has been recognized. The authors administered a 5-hour oral glucose tolerance test (GTT) to 28 depressed patients and 21 healthy volunteer control subjects and measured serum glucose as well as plasma insulin and glucagon responses. Depressed patients demonstrated significantly higher basal glucose levels, greater cumulative glucose responses after the GTT, and larger cumulative insulin responses after the GTT than control subjects. Values for cumulative glucagon did not significantly differ between groups. These findings indicate the presence of a functional state of insulin resistance during major depressive illness and suggest the presence of a more generalized biological disturbance in some depressed patients.

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An association between depression and altered glucose utilization has been noted for some time (1–5). For example, some diabetic patients demonstrate elevated blood sugar levels during a depressive episode (6–8). One group of investigators (9) reported complete remission of diabetic symptoms in 57% of patients with recent-onset, non-insulin-dependent diabetes after the administration of two ECTs, but others (8, 10) have reported a decrease in hyperglycemia after treatment with ECT in depressed diabetic patients.

In studies with nondiabetic depressed patients, several investigations using the insulin tolerance test (4, 11–14) have demonstrated a blunted hypoglycemic response. This finding has been interpreted as indicating a functional state of insulin resistance in depression. In addition, several groups (3, 4) have reported diminished glucose utilization during a glucose tolerance test (GTT) in depressed patients. For example, van Praag and Leijnse (3) demonstrated that almost 50% of their depressed patients had lower glucose utilization after an oral GTT than did control subjects; patients with endogenous depression who improved with medication were especially likely to demonstrate decreased glucose utilization. In 1968 Mueller et al. (4) used an intravenous GTT in patients with different subtypes of depression and observed diminished glucose tolerance in 50% of 42 patients with bipolar (manic-depressive) disorder and psychotic depression but not in patients with neurotic depression. In the Mueller et al. study, however, some of the patients were taking lithium, which may affect glucose utilization (15, 16), and no healthy control subjects were evaluated.

More recently, Wright et al. (14) administered a 60-minute intravenous GTT to 18 drug-free patients with unipolar depression and 14 normal control subjects. Although they found no overall difference in basal glucose or glucose utilization rates, plasma insulin levels were significantly higher in depressed patients at baseline and up to 20 minutes after glucose injection. Wright et al. concluded that their findings demonstrated a form of insulin resistance.

Because these early studies varied widely in patient selection and methodology, direct comparison of results between studies is difficult. In an effort to more fully explore the possibility of insulin resistance in depressive illness, we performed a 5-hour oral GTT in carefully selected patients and healthy volunteers and measured serum glucose and plasma insulin and glucagon responses.

METHOD

Twenty-eight outpatients (12 men and 16 women) from the Depression Research Unit of the Hospital of the University of Pennsylvania were evaluated. All met diagnostic criteria of *DSM-III* for major depression;

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TABLE 1. Age and Hamilton Depression Scale Scores of 28 Patients With Major Depression and Age of 21 Normal Control Subjects Before Administration of Oral Glucose Tolerance Test

	Age (years)			Hamilton Score	
Group	Mean	SD	Range	Mean	SD
Depressed patients (N=28)	38.1[a]	13.0	18–68	25.3	3.6
Men (N=12)	38.9[b]	15.2	18–68	—	—
Women (N=16)	37.5	11.6	18–62	—	—
With melancholia (N=21)	40.6	13.5	18–68	26.5[c]	3.1
Men (N=10)	39.8	16.4	18–68	—	—
Women (N=11)	41.4[d]	11.1	28–62	—	—
Without melancholia (N=7)	30.6	8.0	18–41	21.6	2.2
Men (N=2)	34.5	9.2	28–41	—	—
Women (N=5)	29.0	8.1	18–40	—	—
Control subjects (N=21)	30.1	10.0	21–56		
Men (N=15)	29.2	8.8	21–56		
Women (N=6)	32.5	13.3	21–54		

[a] Signficantly older than control subjects (Welch's T=2.33, df=47, p=0.02).
[b] Significantly older than male control subjects (Welch's T=2.08, df=25, p=0.05).
[c] Significantly higher than mean score of nonmelancholic patients (Welch's T=3.84, df=26, p=0.001).
[d] Significantly older than nonmelancholic women (Welch's T=2.22, df=14, p=0.04).

21 had depression with melancholia and seven did not. Descriptive features of the patient groups are given in table 1. Diagnostic assessments were performed independently before endocrine testing by two research psychiatrists (A.W. and J.D.A.) using a semistructured diagnostic interview. Before endocrinologic evaluation all patients had a minimum score of 20 on the 21-item Hamilton Rating Scale for Depression (17); their mean ± SD score was 25.3 ± 3.6 (range=20–31). Fourteen patients reported decreased appetite, four noted increased appetite with carbohydrate craving, and 10 denied alterations in appetite at the time of initial evaluation. Patients with dysthymic or manic-depressive (bipolar I) disorder were specifically excluded. All patients had been drug free for a minimum of 2 weeks before testing, and many had been drug free for longer periods. The women were not taking oral contraceptives; no patient had ever received a slow-release neuroleptic agent; and none had taken lithium carbonate within 6 months or received ECT within 2 years of testing. Patients were without physical illness and had no clinically significant laboratory abnormalities. None had a history of endocrinopathy, major medical illness, or acute weight change (5 lb. in the previous 4 weeks), and all were within 15% of their ideal body weight. Finally, all subjects had normal fasting blood sugar levels of less than 100 mg/dl.

The control subjects were 21 drug-free healthy volunteers (15 men and six women) who were studied under similar conditions (table 1). All were free of medical illness, had no history of psychiatric illness or endocrinopathy, and had no family history of major depression or diabetes mellitus. None of the subjects in our study was using steroid preparations, and the women were not taking oral contraceptives.

All subjects participated after providing written informed consent. Three days before the oral GTT all subjects were told to follow a minimum 250-g carbohydrate diet providing a minimum of 2,000 calories/day. Because the study was carried out with outpatients, compliance with this regimen could not be directly monitored. After an 8-hour fast, subjects were admitted to the Clinical Research Center and placed at bed rest. At 8:30 a.m. a 19-gauge indwelling needle was inserted into an antecubital vein and an intravenous solution of 0.9% normal saline was given to keep the vein open. Three consecutive baseline blood samples were obtained at 15-minute intervals for basal concentrations of serum glucose and plasma insulin, glucagon, human growth hormone (GH), and cortisol in order to assess the subjects' accommodation to experimental conditions.

Subjects then drank a standard solution of 100 g of glucose in 300 ml of solution over a 5-minute period. Blood samples were then obtained through a three-way stopcock device 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 minutes after the oral GTT for determination of serum glucose and plasma insulin and glucagon concentrations.

Glucose concentrations were measured by using glucose-oxidase-derived techniques (18). Insulin was measured by means of a radioimmunoassay technique with insulin antibody prepared from guinea pigs. The lower limit of sensitivity of the assay was 0.2 ng/ml, and the intra- and interassay coefficients of variation were 6.0% and 9.0%, respectively. Glucagon was measured by means of a radioimmunoassay technique with glucagon antibody prepared in rabbit. The lower limit of sensitivity of the assay was 0.25 ng/ml, and the intra- and interassay coefficients of variation were 3.6% and 5.9%, respectively. We determined GH by means of a double antibody radioimmunoassay technique with a kit from Cambridge Nuclear, Billerica, Mass. The lower limit of sensitivity was 0.8 ng/ml, and the intra- and interassay coefficients of variation were 8.4% and 14.8%, respectively. Cortisol was measured by means of a single antibody technique with a kit from Micromedics, Inc., Horsham, Pa. This method involves the use of polypropylene assay tubes treated with an antibody to cortisol produced in rabbits. Bound cortisol ^{125}I-histamine-antibody complexes are separated from free antigen by aspiration and washing of the assay tube. The lower limit of sensitivity of the assay was 2.5 μg/dl; the intra- and interassay coefficients of variation were 7.7% and 10.8%, respectively.

Basal concentrations of GH and cortisol were determined by radioimmunoassay techniques as described previously (19, 20). Insulin and glucagon were measured in the Diabetes Research Center Laboratory; GH and cortisol concentrations were measured in the Endocrine Research Laboratory of the Department of Psychiatry at the University of Pennsylvania. Assays were simultaneously performed on samples from patients and control subjects. All samples from a single subject were assayed together in duplicate.

The glucose, insulin, and glucagon responses to the oral GTT were examined according to four response measures: 1) basal concentrations, 2) the centered cumulative response after the oral GTT, 3) the maximum increase above baseline after the oral GTT, and 4) the peak concentration reached after the oral GTT.

The centered cumulative response was computed by using the trapezoidal approximation to the total integrated area under the response curve after subtracting the baseline value. In this computation, time was defined in 30-minute units: unit 0 (0 minutes), unit 1 (30 minutes), unit 2 (60 minutes), up to unit 10 (300 minutes). All measurements were centered so that at time unit 0 the response value was 0 for all subjects. In this regard, any correlation between baseline values and response measures would be attributable to physiological associations and not to the method of measurement. To this end, we examined within-group correlations to ascertain the appropriateness of performing analysis of covariance (ANCOVA) on differing baseline values. However, ANCOVA-adjusted analyses are appropriate only if within-group correlations between basal values and oral-GTT-induced response measures exist and are consistent.

The technique of general linear models was used to compare the mean values of the basal and response measures between patient and control groups for glucose, insulin, and glucagon. Additionally, an analysis of variance (ANOVA) with repeated measures over time was used to compare the overall response curves of groups. For parametric two-group comparisons, p values were based on Welch's T test for groups with unequal variances if the hypothesis of equal variance was rejected at the 0.05 level of significance. Nonparametric tests for differences in means were also performed by using the Mann-Whitney U test, and parallel analyses were performed on log- and rank-transformed data to ensure that our conclusions were not dependent on the assumption of normal populations.

The relationship between age and each of the glucose, insulin, and glucagon responses was examined by using regression and correlation analyses in order to determine the appropriateness of using ANCOVA to adjust for differing mean ages in the subject groups. Pearson and Spearman correlation coefficients were calculated to determine if there were any relationships among the responses to oral GTT and basal GH and cortisol concentrations.

Finally, a three-group analysis was performed that compared control subjects with depressed patients after the patients had been separated into melancholic and nonmelancholic subgroups.

RESULTS

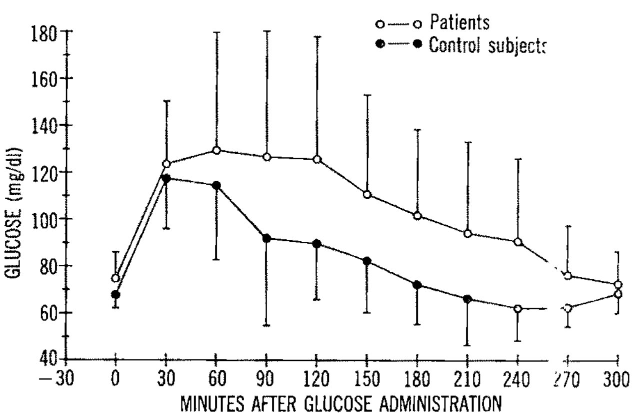
Table 2 summarizes the analyses performed on the basal and response measures for glucose, insulin, and glucagon. Figures 1–3 illustrate the subjects' response profiles after administration of the oral GTT.

TABLE 2. Glucose, Insulin, and Glucagon Response Measures After Oral Glucose Tolerance Test in 28 Patients With Major Depression and 21 Normal Control Subjects

	Control Subjects		Patients		
Response Measure	Mean	SD	Mean	SD	p[a]
Glucose (mg/dl)					
Basal	67.80	5.60	74.70	11.30	0.007
Centered cumulative response	152.00	103.30	312.70	246.30	0.004
Maximum	61.20	23.60	73.20	37.80	0.181
Peak	129.20	24.30	152.60	48.60	0.032
Insulin (ng/ml)					
Basal	0.77	0.20	0.65	0.34	0.087
Centered cumulative response	12.50	5.40	19.90	11.90	0.006
Maximum	3.19	1.25	4.40	2.41	0.029
Peak	3.99	1.32	4.98	2.48	0.081
Glucagon (pg/ml)					
Basal	259.30	102.90	251.60	162.60	0.840
Centered cumulative response	−286.60	215.20	−511.10	760.90	0.147
Maximum	−55.40	37.50	−101.00	102.40	0.037
Peak	−198.40	90.20	−150.60	92.30	0.077

[a] General linear models technique.

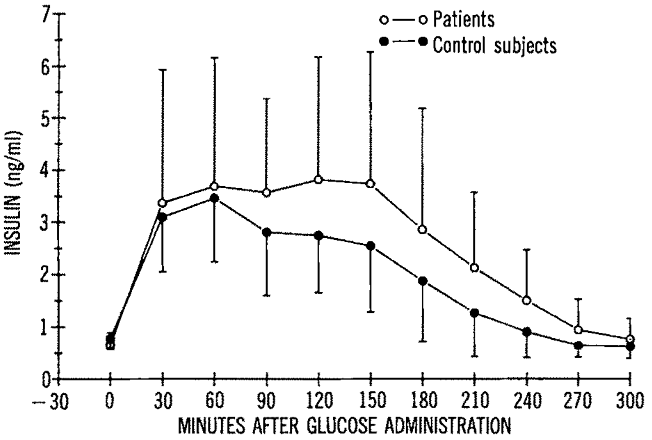
FIGURE 1. Mean±SD Glucose Responses After Oral Glucose Tolerance Test in 28 Depressed Patients and 21 Healthy Control Subjects[a]



[a] Patients had greater cumulative glucose levels over time (Welch's T=3.11, df=38, p=0.004), and there was a significant Group by Time interaction effect (F=3.21, df=10, 470, p=0.02 after Greenhouse-Giesser adjustment). (The repeated measures test for a difference in the overall glucose level yielded F=10.25, df=1, 47, p=0.002.)

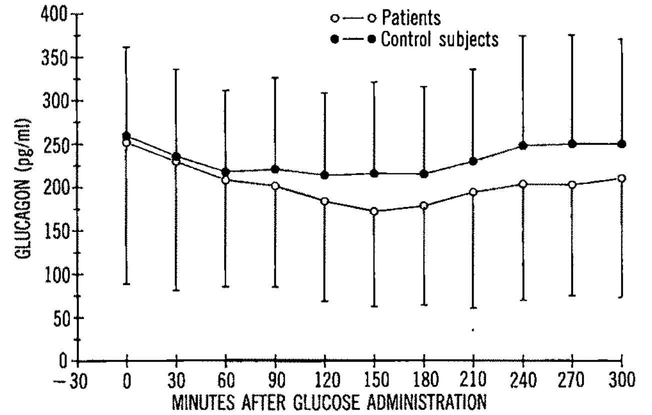
The depressed patients had slightly but significantly higher basal glucose levels and greater cumulative glucose levels over time after the oral GTT. The patients also had a greater cumulative response of insulin after the oral GTT as measured by both the insulin centered cumulative response and the maximum insulin value. The maximum glucagon value was significantly greater in depressed patients than in control subjects, indicating that the depressed patients had a larger mean maximum nadir after glucose administration. However, values for the cumulative glucagon response did not differ between the two groups.

FIGURE 2. Mean±SD Insulin Response After Oral Glucose Tolerance Test of 28 Depressed Patients and 21 Healthy Control Subjects[a]



[a]Patients had a greater centered cumulative insulin response over time (Welch's T=2.92, df=47, p=0.006).

FIGURE 3. Mean±SD Glucagon Decrement After Oral Glucose Tolerance Test in 28 Depressed Patients and 21 Healthy Control Subjects[a]



[a]The maximum glucagon decrement was significantly greater in patients (Welch's T=2.17, df=36, p=0.037), but cumulative glucagon decrements were not significantly different between groups.

The repeated measures ANOVA for the glucose response profile demonstrated a significant Group by Time interaction effect, reflecting the different shapes of the glucose response curves (figure 1). The ANOVA for the insulin response curve demonstrated a significant time effect for both groups (F=48.80, df=10, 470, p=0.001) as well as a clear trend for higher overall insulin levels in the patients (figure 2). The repeated measures ANOVA for the glucagon response curve yielded no significant differences between groups in cumulative glucagon decrements (figure 3).

Nonparametric group comparisons yielded similar results. In addition, analyses performed on log-transformed data yielded no substantive differences from those obtained by the parametric tests.

Within-group correlation analyses demonstrated a significant correlation between glucose centered cumulative response and insulin centered cumulative response (r=0.71, N=21, p<0.01) after the oral GTT in the control group. In contrast, this correlation was smaller and nonsignificant in the patient group (r=0.32, N=28, p=0.09). However, the magnitude of the Spearman coefficient (rho=0.54, p<0.01) suggests that the Pearson test results may be artificially low due to several extreme response values.

A relatively strong linear relationship was observed between the basal insulin and the insulin centered cumulative response values after the oral GTT (r=0.69, N=28, p<0.01) and between the basal glucagon and glucagon centered cumulative response values after the oral GTT (r=−0.73, N=28, p<0.01) in patients. Furthermore, we found a significant correlation between basal insulin and the glucose centered cumulative response (r=0.45, N=28, p=0.02) in the patients. None of these correlations was significant in the control group.

In contrast, a negative correlation between basal cortisol and both the glucose centered cumulative response and the insulin centered cumulative response measures was observed in the control group. However, no such relationship or trend was observed in the patient group. The mean±SD baseline cortisol and GH values for the patients and control subjects were 16.5±10.5 μg/dl versus 18.3±11.5 μg/dl (Welch's T=0.55, df=44, p=0.58), and 2.2±1.8 ng/ml versus 4.6±6.6 ng/ml (Welch's T=1.49, df=20, p=0.15), respectively.

The influence of severity of depression, as measured by the Hamilton depression scale, on glucose, insulin, and glucagon measures during the oral GTT was assessed by means of a correlation analysis. We observed a significant Pearson correlation between the glucose centered cumulative response and Hamilton scale score (r=0.41, N=28, p=0.03). No significant correlations were observed between the Hamilton scale score and insulin or glucagon centered cumulative response measures. To ensure that the significant Pearson correlation between glucose centered cumulative response and Hamilton scale score was not due to extreme values, we computed the Spearman rank correlation and found even stronger evidence of a positive relationship (rho=0.49, p=0.008).

This apparent significant relationship between Hamilton scale score and glucose centered cumulative response must be viewed with some caution. We observed a relatively strong correlation between age and Hamilton scale score (r=0.68, N=28, p<0.0001) and some evidence of a correlation between age and glucose centered cumulative response (r=0.34, N=28, p=0.08). We then carried out an analysis for the partial correlation of glucose centered cumulative response and Hamilton depression scale score, controlling for age by using multiple linear regression. With this analysis, we obtained an r of 0.26 (N=28, p=0.19). Thus, although an additional 7% of the variability in glucose centered cumulative response not explained by age could be explained by Hamilton scale score, the relationship failed to reach statistical significance.

Since previous neuroendocrine studies have suggested that patients with melancholic depression may represent a diagnostically homogeneous subgroup of patients who are more likely to demonstrate endocrinologic abnormalities (21–23), we examined this group of patients separately. We found that the melancholic patients differed significantly from the control subjects in glucose centered cumulative response (Welch's T=3.49, df=29, p=0.002) and insulin centered cumulative response (Welch's T=2.73, df=26, p=0.02) after the oral GTT, whereas the response values of nonmelancholic patients were closer to those of the control group.

Finally, depressed patients were somewhat older (mean±SD age=8 ± 13 years) than the control subjects (30 ± 10 years), so correlation analyses were performed between mean age and each basal and response measure. Age was not correlated with any of the measures in the control group (all p values were greater than 0.40 and all r values were less than 0.19). However, the patients' age was positively correlated with basal glucose (r=0.47, N=28, p=0.01) but not with glucose centered cumulative response. Moreover, the correlation between age and glucose centered cumulative response for control subjects was slightly negative, indicating that an age ANCOVA was not appropriate. Similarly, there were no significant correlations between age and any insulin measure.

DISCUSSION

Serum glucose concentrations after the oral GTT remained elevated for a longer time in depressed patients than in control subjects (figure 1). Consequently, even though the maximum glucose values after the oral GTT were similar for both groups, the mean cumulative glucose response (centered cumulative response) of patients was twice that of control subjects (table 2). In addition, the rate of rise for serum glucose after the oral GTT was similar for patients and control subjects up to 60 minutes, after which the patients had higher glucose values for each time point until the 300-minute sample. These results indicate an impaired glucose utilization in the depressed patients.

Basal insulin values were similar in patients and control subjects, and insulin secretion during the initial 60 minutes after the oral GTT was comparable for both groups. However, the mean insulin centered cumulative response after the oral GTT was significantly greater in the depressed patients than in the control subjects (table 2), indicating that the patients had no defect in insulin secretion from the pancreatic beta islet cells in response to glucose administration. However, the fact that glucose levels remained elevated after 60 minutes despite the pronounced increase in insulin secretion is indicative of a relatively insulin-resistant state in depression.

Plasma glucagon measurements revealed a larger nadir after the oral GTT in the depressed patients (table 2), and this represents an expected compensatory response to higher glucose levels after the oral GTT (figure 3). Taken together, these findings indicate that both insulin and glucagon secretion in depressed patients respond appropriately to elevations in plasma glucose after the oral GTT.

Several issues need to be considered in the interpretation of the present findings. Glucocorticoids have an anti-insulin action resulting in hyperglycemia. Some investigators (21, 24, 25) have reported higher basal cortisol levels in depressed patients than in control subjects, and one possible explanation for our observation of relative insulin resistance might be elevated serum cortisol levels in depressed patients. However, in the present study cortisol levels were not significantly different between patients and control subjects. Furthermore, several investigators (24, 25) have also reported a correlation between relative insulin resistance (after insulin tolerance testing) and a modestly elevated serum cortisol level in depressed patients. Similarly, GH has complex effects on carbohydrate metabolism and may also contribute to insulin resistance (26, 27). However, in the present study we observed no differences in basal GH levels between patients and control subjects and found no significant correlation between basal GH and glucose centered cumulative response or insulin centered cumulative response after the oral GTT in either patients or control subjects. We also observed no significant correlation between basal cortisol and glucose centered cumulative response or insulin centered cumulative response measures in the patients. However, we did note significant negative correlations between basal cortisol and glucose centered cumulative response and insulin centered cumulative response after the oral GTT in control subjects. It must be emphasized that cortisol and GH values represented single time point basal assessments. It is conceivable that pulsatile episodes of cortisol or GH secretion might have been missed in this paradigm.

Dietary and weight changes occurring during depression might conceivably have influenced glucose and insulin utilization in our subjects. For example, obese subjects demonstrate a diminished insulin sensitivity and altered glucose tolerance, which is probably the result of insulin resistance at peripheral tissue receptors (28), and some patients with anorexia nervosa have enhanced insulin sensitivity and increased glucose utilization (29). However, in the present study both the depressed and control subjects were within 15% of their ideal body weight, and the modest weight gains or losses reported by the patients were not acute in nature and not likely to have substantially affected overall carbohydrate tolerance. Furthermore, all subjects were placed on a standardized diet for at least 3 days before the oral GTT in order to minimize dietary differences between patients and control subjects. Glucose tolerance normally decreases with increasing age (30). Since the mean age of our patients was somewhat greater than that of our control subjects, we paid particular attention to this factor as a possible contributor to the diminished glucose and insulin tolerance observed in the patients. Although basal glucose was positively correlated with age in the patient group ($r=0.47$, $N=28$, $p=0.01$), all other glucose, insulin, and glucagon measures after the oral GTT were not significantly related to age in either patients or control subjects, indicating that age per se was not responsible for the present findings.

The depressed patients in this study had overall glucose and insulin response curves to glucose administration similar to those of patients with non-insulin-dependent (type II) diabetes, who demonstrate insulin resistance at peripheral tissue sites (31–33). This observation suggests the possibility that depressed patients may also manifest a similar mechanism for insulin resistance. DeFronzo et al. (31, 33), using the euglycemic clamp technique in patients with type II diabetes, demonstrated that the most important site of insulin resistance was in muscle tissue and that resistance resulted from a diminished insulin receptor concentration.

In conclusion, the demonstration of larger glucose and insulin cumulative responses after the oral GTT in depressed patients than in healthy control subjects indicates a functional insulin-resistant state. These findings suggest the presence of a more generalized biological disturbance in some patients with major depression.

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Commentary

Dysfunctions in Public Psychiatric Bureaucracies

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The author describes common dysfunctions in public psychiatric organizations according to the model of bureaucracy articulated by Max Weber. Dysfunctions are divided into the categories of goal displacement, outside interference, unclear authority structure and hierarchy, and informal relations in the work place. The author emphasizes the bureaucratic nature of public psychiatry and the need for mental health professionals to understand the dysfunctions of the organizations in which they work, including the impact of these dysfunctions on the provision of quality care.

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The word "bureaucracy" has a bad reputation and is often used pejoratively to describe a dysfunctional organization marked by officialism, red tape, and proliferation. Even dictionaries offer negative meanings of the word "bureaucracy," e.g., "government characterized by adherence to inflexible rules of operation, . . . any administration in which the need to follow complex procedures impedes effective action" (1). It has been further suggested that the structure and tradition of bureaucracies turn otherwise decent people into "bureaucratic personalities," characterized by negativism, rigidity, and arrogance (2). Conceptually, the bureaucracy model of organizations has also been criticized. Social engineering groups claim that bureaucracies are inflexible, ritualistic, and, at times of rapid change, uncreative and unresponsive. Human relations groups frequently contend that bureaucracies negate the individual's autonomy and stifle the spontaneity and self-realization of their employees.

However, according to Max Weber, who originally coined the term, a bureaucracy is the most effective type of organization based on legal-rational authority, as distinguished from organizations of people bound together by either charismatic power (i.e., on the basis of the leader's personal qualities) or traditional authority (i.e., on the basis of the inherited status of the leader). A bureaucratic organization is characterized by 1) clearly stated goals, 2) organizational independence from private matters and outside interference, 3) a hierarchical authority structure in which the appointment of members is made exclusively on the basis of expertise, technical knowledge, and skills, and 4) formal relationships among organizational members, so that personal or interpersonal elements do not interfere with the organization's operations (3, 4). In a bureaucracy, rules and procedures are the means to achieve goals, and their purpose is to make the organization more rational and effective.

Mental health professionals like to view psychiatric organizations as nonbureaucratic or as based on a social interaction of human beings, who function more by means of mutual agreements and relationships than by means of pyramidal authority and who through participation, consultation, and cooperation shape the organization more than technology or policy does (5). Although this may be true in small private settings, it certainly does not apply to large-scale organizations such as hospitals or community mental health centers, particularly those which are operated under public auspices (6). To a large extent, this is because as standards of care become more specific and regulated, and as economic and quality controls increase, the tasks that psychiatric professionals perform in institutional settings become better understood and more predictable, routinized, and programmed (7, 8).

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Most mental health professionals pay little attention to the problems of the organizations in which they work (9). In this regard, Greenblatt has stressed the need to understand psychiatric organizations and has coined the term "social system clinicians" for those who take the responsibility for diagnosing and influencing organizations with the goal of leading them to greater productivity and higher morale (10). The purpose of this paper is to describe examples of common dysfunctions in public psychiatric organizations by examining the major principles of the model of bureaucracy as it was articulated by Max Weber (3, 4).

GOAL DISPLACEMENT

The bureaucracy model requires clear organizational goals. In general terms, the official goal of most public psychiatric bureaucracies is the provision of cost-effective, quality mental health services to individuals in need, regardless of their ability to pay. A dysfunction occurs when this relatively straightforward mission is displaced by other, often unspoken goals (11–13). An extreme example of goal displacement in a public psychiatric organization occurs when the organization becomes a tool for either police or sociopolitical power. This dysfunction, which has occurred in some dictatorships, consists of using psychiatric institutions for the imprisonment of individuals considered to be social deviants or political or ideological dissidents (14, 15). Obviously, this constitutes an aberration of public psychiatry. However, there are other, less extreme examples of dysfunctions related to the misuse of mental health organizations.

For instance, each year there are several thousand people in the United States who are hospitalized in public psychiatric institutions with "dangerousness to others" used as the criterion for their civil commitment. The controversy about the definition of dangerousness is compounded by the inability of psychiatrists to predict dangerousness accurately. A dysfunction occurs when the definition of dangerousness is interpreted to apply, for example, to socially disabled individuals whose primary disability is not mental illness, such as those with sociopathic behavior. This situation is often triggered by policy makers' genuine concern about protecting disabled citizens or ensuring the safety of the public, and it is facilitated by the fact that, historically, psychiatry has been asked to deal with social problems. The end result, however, is a goal-displacement dysfunction in the organization, since limited public psychiatric resources have to be used to handle populations with different needs who are involved with the criminal justice system (16).

As another example, policy makers may resort to using public psychiatric organizations for employing people, particularly low-level, unskilled workers. This action results in the displacement of the organization's primary goal by a sociopolitical mission. The employment of large numbers of persons in low-paying jobs, regardless of their skills, is generally cheaper than their maintenance on public welfare. Furthermore, it has the political gain of reducing unemployment figures and securing the support of unions, which also benefit from the increase in dues-paying members. This misuse of the organization, however, certainly results in a dysfunctional bureaucracy and negatively affects the delivery of quality care (9).

Another dysfunction develops when senior professionals, such as psychiatrists and psychologists, see their primary mission in the organization in terms of research and training rather than direct patient care. As a result, the clinical tasks are relegated to psychiatric residents and other less experienced mental health professionals who provide "cheap labor" but are less qualified to treat the most disturbed patients (13). In this example, the primary organizational goal of patient care is displaced by teaching and research.

OUTSIDE INTERFERENCE

The bureaucracy model requires organizational independence from outside interference. Although public psychiatric organizations are by definition influenced by a set of environments, including the community and the political and economic milieu, dysfunctions occur when these environments interfere with clinical definitions of treatment and outcome and force the institution to meet external priorities rather than the needs of the patients (17, 18). Mollica (19) described a number of areas of environment-related policy contradictions that have threatened the stability of public psychiatric organizations. For instance, the financial pragmatism of government in the past has undermined public psychiatry's ability to guarantee adequate treatment by shifting resources from the public sector to private vendors, which do not subject themselves to public monitoring and do not address the needs of public patients. As a result, certain groups of public patients—minorities, the chronically ill, and the elderly—often receive substandard care consisting primarily of psychosocial support from nonprofessional mental health workers.

A different but related dysfunction occurs when, in order to cope with environmental financial constraints, public psychiatric organizations develop the unspoken policy of treating larger proportions of paying or insured patients, the implication being that less public subsidy funding will be required. As a result, however, indigent patients are discouraged from seeking services, and the primary goal of the organization is undermined (20). Also, due to economic factors, in recent years there has been an increasing demedicalization of public psychiatric programs and a failure to provide the clinical technology necessary to address a number of psychiatric disorders (21).

Talbott (22) has addressed the issue of undue outside interference in public psychiatry by policy makers, particularly at times of budgetary constraints. Focusing on the chronically mentally ill, he has pointed out, for instance, that the forces which resulted in the ultimate depopulation of state hospitals were political, economic, and legal rather than clinical.

In most states, the administrative reorganization of the care of mental illness, mental retardation, and substance abuse into three separate and autonomous systems is another example of a dysfunction in public psychiatry associated with outside interference. By disregarding the realities of the patients and their needs, this policy has resulted in the fragmentation of public psychiatric services and the failure to provide care to many patients with dual diagnoses, such as those with psychiatric illness and developmental disabilities (23).

UNCLEAR AUTHORITY STRUCTURE AND HIERARCHY

In a bureaucratic organization there is a hierarchical authority. Each office or position is under the control and supervision of a higher one. Every employee is accountable to a superior for his or her own decisions and actions as well as for those of his or her subordinates. In public psychiatric organizations there are two major groups of employees: administrators and clinicians. A common dysfunction occurs when the authority structure lacks coordination between these two components. The unstructured placement of clinical experts under the authority of nonclinical administrators can result in conflicts and problems, particularly if the table of organization does not clearly reflect the day-to-day pattern of work, relationships, and reporting. Unless lines of accountability and areas of responsibility are operationally defined, administrators may possibly be confronted by clinicians who are their subordinates but whose special clinical expertise allows them to dispute their superiors' judgment and authority (24).

It is frequently claimed that there is an inherent conflict between clinical values and administrative ones, between authority based on clinical competence and authority based on the position in the administrative structure (25). Clinical authority is often exercised through professional societies and academic disciplines and is usually regulated by standards set by colleagues (26). The complexities in the evaluation of the performance of the different mental health disciplines make it all the more difficult for an administrator to hold authority over clinical professionals. However, given the increasing standardization of public psychiatric services, it is reasonable to expect clear functional criteria for clinicians and administrators. These criteria should be based on a division of labor and expertise (i.e., clinical versus administrative tasks) and should provide mechanisms for control over performance and means for coordinating roles and preventing them from interfering with each other (7).

Although this is an area not directly related to public psychiatry, Kernberg recently addressed the organizational problems associated with the lack of clear functional criteria for the appointment of psychoanalytic faculty, which is usually politically motivated (27). He sees the consequences in terms of regression and "paranoiagenic" deterioration of the institution. To treat these dysfunctions, Kernberg called for the introduction of bureaucratic principles, such as clear lines of organizational structure and specific criteria for selection of faculty.

INFORMAL RELATIONSHIPS IN THE WORK PLACE

According to the bureaucracy model, effectiveness at work increases as employees' behavior becomes more rational, logical, and clearly communicated. On the other hand, effectiveness decreases as behavior becomes more emotional and unpredictable. In this regard, Freud observed that unstructured groups tend to produce a profound alteration in the individual's behavior—specifically, regression, an increase in inappropriate affect, and a reduction in the individual's intellectual ability. These unwelcome consequences, however, can be prevented by a better organization of the group (28).

Dysfunctions in public psychiatric organizations often occur when their leaders place undue emphasis on employees' informal relations at work, claiming that this is necessary to respond to basic human needs for communication and self-esteem. Often, the result is more unpredictable relationships and more unproductive employees (12). Although some studies have found that positive interpersonal relationships at work are correlated with lower absenteeism and turnover and with higher performance, there is at least similar support for the notion that employee satisfaction results from high performance rather than being the cause of it (29). It is apparent, however, that very little is known about how these difficult-to-measure psychosocial variables may predict work group performance in general and the delivery of psychiatric care in particular.

Training and sensitivity groups for employees have become very common in organizations, particularly in those devoted to mental health care. Often, participating members are encouraged to self-disclose and to be open about their personal affairs. So far, however, there is no evidence to support the usefulness of training groups in an organization, although many participants attend these groups for purposes of novelty and social contact (30). Certainly, what may be useful and therapeutic for the individual is not necessarily useful for the organization (31). While the stated purpose of these groups is to improve morale, attitudes, communication, and group cohesion among the members of the organization, often the end result is a dysfunction in the organization, with increased interpersonal conflicts, role confusion, and distraction from the specific tasks that the job requires (12).

CONCLUSIONS

I believe that most of the dysfunctions in public psychiatric bureaucracies that I have described are due primarily to conflict. Whether the conflicts are the result of goal displacement, unclear lines of accountability, human shortcomings, or outside interference, elimination of conflict is always the goal in a bureaucracy (32). Therefore, to attribute the ills of an organization to its "bureaucratization" misses the point. Instead, one should talk about specific instances of organizational conflict, dysfunctional bureaucracy, or maladministration (12).

It appears that modern psychiatric organizations are increasingly and inevitably bureaucratic—this is particularly true in the public sector (6). The necessity for the bureaucratic model in public psychiatry is grounded in its rationality and its specialized technical expertise. In addition, the bureaucratic model is particularly suitable to large-scale public psychiatric organizations because it provides effective mechanisms for dealing with the increasing controls and regulations being placed on the quality and cost of psychiatric care. Furthermore, the growing standardization of diagnostic criteria and treatment modalities and the emphasis on rules and regulations, backed up by legal and peer review sanctions, have created the need for tighter organizational structure and accountability (6–8).

Nonbureaucratic alternatives, when applied to large-scale organizations, are rare and soon become very expensive, unstable, and short-lived (12). These alternatives, however, may be appropriate for small, unstructured organizations that emphasize the individual's performance over institutional goals (e.g., private practice, small research laboratories). These organizations may be subject to frequent and rapid changes or innovations, they encourage freedom to experiment, and they have little need for uniformity of policies and procedures (9).

A bureaucracy not only is an effective type of organization, as Weber believed, but it can also provide the setting for both constructive human relationships and the individual's creative expression and satisfaction (11). Perhaps to gain and maintain this creativity requires that we, as social systems clinicians, learn more about the workings of public psychiatric organizations, including the types of dysfunctions that can afflict them. This understanding would enable us to better use, control, and improve these institutions, in order to provide the best and most cost-effective psychiatric care possible to all in need, regardless of their ability to pay for it.

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Brief Communications

Low-Dose Neuroleptic Therapy for Children With Childhood-Onset Pervasive Developmental Disorder

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An open study of the therapeutic effects of low-dose neuroleptic treatment was performed on 12 consecutively hospitalized children, aged 7–11, who satisfied DSM-III *criteria for childhood-onset pervasive developmental disorder. While receiving an average dose of 0.04 mg/kg per day of haloperidol or fluphenazine hydrochloride, the patients exhibited significant reductions in hyperactivity and aggressive symptoms and significant improvement in peer relations. This dose of neuroleptic was associated with minimal side effects. The authors conclude that low doses of potent neuroleptics may be effective treatment for some patients suffering from childhood-onset pervasive developmental disorder.*

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The *DSM-III* diagnostic category of childhood-onset pervasive developmental disorder was introduced in 1980 to describe a group of seriously disturbed children who did not satisfy the diagnostic criteria for either infantile autism or schizophrenia. Before 1980 there had been a confusing proliferation of diagnostic terms and subclassifications under the broad umbrella term "childhood schizophrenia." During the 1970s, recognition grew that it was necessary to differentiate between severe mental disorders arising during infancy, of which infantile autism constitutes the prototype, and the psychoses arising in late childhood or adolescence, of which schizophrenia is the prototype. To address a third group of disturbed children, the diagnostic category of childhood-onset pervasive developmental disorder was proposed to include children who exhibit severe impairments in social relationships in association with excessive anxiety, inappropriate affect, resistance to change, and abnormalities in movement, speech, and sensation. Although these children often present with bizarre thinking and preoccupations with fantasies, the diagnosis of childhood-onset pervasive developmental disorder excludes the presence of delusions, hallucinations, or incoherence. At present, little is known about the cause of these disorders, the extent to which they constitute a homogeneous group, or the nosological validity of the diagnosis.

Little has been written about the possible psychopharmacological management of symptoms in pervasive developmental disorder. This deficit, in part, reflects the recent introduction of the diagnostic category. Consistent with our clinical experience, Campbell et al. (1) have reported that psychostimulants are not particularly effective in reducing the behavioral problems of children with symptoms of pervasive developmental disorder and may actually exacerbate some of the autistic-like features of the disorder. Because the cognitive and motoric abnormalities observed in pervasive developmental disorder might be responsive to neuroleptic treatment, we examined the effects of low-dose treatment with incisive neuroleptics on 12 consecutively hospitalized patients who fulfilled *DSM-III* criteria for childhood-onset pervasive developmental disorder or atypical pervasive developmental disorder. We now report that this treatment results in significant reductions in hyperactivity and impulsivity, improvement in peer relations, and minimal side effects.

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METHOD

All patients were hospitalized on the Children's Psychiatric Inpatient Unit at Johns Hopkins Hospital in 1984–1985. On admission, all patients received detailed psychological testing, including WISC-R and projective tests such as the Sentence Completion Test, Rorschach, and Thematic Apperception Test (TAT) cards. The diagnosis of childhood-onset pervasive developmental disorder was based on *DSM-III* criteria. Detailed medical examinations were carried out, including determination of hematologic and electrolyte levels, urinalysis, and EEG. Other diagnostic procedures were performed as indicated to rule out metabolic or structural etiology of the psychiatric disorder. Informed consent was provided by the parent or legal guardian for each child before the study was carried out.

Behavior was monitored daily, and the Hopkins Child Behavioral Score (in preparation) was applied to each child. This scale is a rating instrument that assesses primarily peer interactions and "prosocial" behaviors; it has a high degree of interrater reliability ($r=0.90$). Hopkins behavioral scores range from 0 to 57 points. Normative data on 158 patients aged 5 to 14 have been developed to obtain percentile rankings on the Hopkins behavioral score. In addition, the Conners behavioral checklist (2) was used: the conduct scale (scored 0–33), a measure of aggression, was applied by nursing staff during evening play activities, and the hyperactivity scale (scored 0–30) was administered by teachers during class in the unit's school. All results are expressed as mean±SD, and statistical significance was determined by one-tailed t test. Seven to 10 days of baseline behavioral observations were obtained on each patient while he or she was free of medication. The patients were then given oral doses of haloperidol or fluphenazine hydrochloride, administered in divided doses, beginning at 0.02 mg/kg per day. Neuroleptic dose was increased at 3–5-day intervals on the basis of behavioral response.

RESULTS

The patient group consisted of 12 children, 7 to 11 years old (mean age=9.1 years). Ten were boys and two were girls. Eight satisfied *DSM-III* criteria for childhood-onset pervasive developmental disorder, and the remaining four satisfied criteria for atypical pervasive developmental disorder. The mean±SD full-scale IQ score for the group was 85.3±7. Although none of the children in our study exhibited evidence of frank hallucinations or delusions, all exhibited marked disturbances in peer interactions, preoccupation with fantasies, inability to tolerate change, and aggressive outbursts. The projective tests generally indicated fragile reality testing with disorganized thought processes and bizarre ideation.

On the basis of clinical assessment of response, the optimal mean±SD doses of haloperidol and fluphenazine hydrochloride for this group were 0.04±0.01 mg/kg per day or 1.3±0.7 mg/day, respectively. Objective ratings confirmed the clinical impression. During baseline observations, the mean±SD children's Conners hyperactivity score was 11.5±3.3; this fell to 6.0±1.4 on optimal treatment ($t=5.33$, $df=11$, $p<0.01$). Similarly, the conduct scores before treatment of 14.4±3.8 fell to 5.4±2.2 ($t>7.14$, $df=11$, $p<0.01$). As an index of peer interactions and behavioral organization, the Hopkins behavioral scores rose significantly ($t>3.96$, $df=11$, $p<0.01$) during treatment: baseline scores placed the patients in the 28±17 percentile, but treatment scores placed them at the 58±20 percentile.

To assess the impact of behavior management and the milieu of the ward, neuroleptics were temporarily discontinued in three of the 12 patients. On withdrawal of the medication, the behavior problems with which these patients initially had presented recurred. During neuroleptic withdrawal, the patients were also less responsive to behavior modification and the milieu. Neuroleptics were reinstituted at the previous low doses, and the patients once again showed a more positive response to treatment. Of particular note is that none of the three patients displayed any withdrawal symptoms. This may reflect the fact that the patients were all receiving low doses of neuroleptics.

Five of the patients were given the projective tests a second time while receiving optimal doses of neuroleptics. Generally, these children exhibited remarkable improvements in reality testing, thought organization, and coherence in the themes of their productions. For example, one 10-year-old girl's responses to projective testing before neuroleptic treatment revealed a primitive quality to her way of dealing with emotions. This immaturity colored her views of the world around her, resulting in distortions and diffusion of perceptions. Her human figure drawings provoked a great deal of anxiety about sexual maturation and the concomitant bodily changes. This anxiety was also reflected in her TAT responses, in which a picture of a pregnant woman precipitated a series of continuous, perseverative stories about pregnancy, childbirth, and death that persisted in subsequent cards. Reevaluation of this girl while she was receiving optimal doses of haloperidol revealed considerable improvement. Although the basic themes were not changed, she was much more organized in dealing with her fears and anxieties. Her elaborations on the themes of pregnancy and childbirth were not so disturbed and she no longer had morbid thoughts. Her self-drawing, which before treatment was depicted as nude, was now more appropriately dressed in a long gown.

Side effects were remarkably infrequent with low-dose neuroleptic treatment. Three children exhibited transient drowsiness in the initial phase of treatment, but this dissipated over time and did not interfere with their cognitive performance. Two children experienced mild extrapyramidal symptoms with rigidity and cogwheeling during the initial few days of treatment with haloperidol. In both cases, these symptoms were alleviated by oral diphenhydramine and did not recur with the discontinuation of the antiparkinsonian drug.

Seven of the 12 children, who on admission had been referred for evaluation for long-term residential care, were able to return home and attend schools in their community. The other five were also able to return home temporarily while plans were being made for residential placement. However, in the latter group, additional factors such as an unstable home environment and a lack of parental involvement contributed to the necessity for seeking residential placement.

DISCUSSION

Bender (3) first described "childhood schizophrenia" with reference to a very broad and ill-defined group of severe disorders of childhood. Childhood-onset pervasive developmental disorder was introduced in *DSM-III* to include children who could not be characterized as autistic and did not fulfill criteria for schizophrenia. More recently, Cohen et al. (4) suggested a need for revision of this diagnostic category of pervasive developmental disorder. These investigators also questioned the justification of using the age at onset as the differentiation between infantile autism and childhood-onset pervasive developmental disorder, suggesting that the age at onset be more appropriately termed the "age of recognition" (5). Thus, there remains at present debate as to whether childhood-onset pervasive developmental disorder can or should be clearly distinguished from infantile autism.

Little has appeared in the psychiatric literature directly addressing the psychopharmacological management of symptoms in childhood-onset pervasive developmental disorder. The historical confusion surrounding diagnosis of the severely disturbed child is mirrored in the pharmacological studies that have been carried out in this population. The principal groups that have been studied so far are children with childhood schizophrenia, infantile autism, mental retardation, and hyperkinesis with learning disabilities. However, it is often difficult to discern which of these groups or which mixture of these groups was studied. This difficulty stems in large part from the fact that studies done before the publication of *DSM-III* often used *DSM-II* or *ICD-9* nomenclature, which placed autistic children under the classification of childhood schizophrenia and did not have childhood-onset pervasive developmental disorder as a separate diagnostic category.

Among the large variety of neuroleptics available, haloperidol has been relatively well studied by several investigators in the management of childhood psychotic disorders. In most of these studies, haloperidol proved to be significantly superior to placebo when used at low doses and was usually better than psychotropic medications from other classes, such as psychostimulants and lithium (6, 7). Similarly, haloperidol resulted in significant decreases in behavioral symptoms and in general clinical improvement in autistic children (8). Although current evidence does not suggest any clear superiority of a particular neuroleptic, once corrected for potency in the management of psychotic symptoms, the incisive neuroleptics such as haloperidol or fluphenazine generally have less sedating effects that could interfere with alertness and cognitive functions, especially in the classroom setting (9).

From our series of 12 inpatients in an open study, clinical observations and rating scale assessments indicate remarkable improvement in peer interactions, reduction in autistic-like behaviors, improved reality testing, and decrements in impulsivity and hyperactivity with low-dose neuroleptic treatment. Preoccupation with fantasies and morbid interests as well as resistance to change with perseveration appeared to be considerably reduced, as supported by follow-up projective testing in five of the 12 patients.

A noteworthy feature of these results is that the patients responded to remarkably low doses of the incisive neuroleptics, haloperidol and fluphenazine hydrochloride; the mean total daily dose was less than 2 mg. Although we were not able to obtain measurements of serum levels of neuroleptics in these patients, in a study of a comparable age group of patients receiving similar doses of haloperidol for treatment of Tourette's disorder (10), the serum levels were observed to be quite low—at least 10 times lower than those typically associated with therapeutic response in adults suffering from schizophrenia. Because there is evidence of a correlation between serum levels of haloperidol and the presence and severity of extrapyramidal symptoms in children and adults (11), the low prevalence of extrapyramidal symptoms in our patient population was not unexpected. Only two patients exhibited mild and temporary extrapyramidal symptoms, and neither required maintenance treatment with anticholinergic drugs.

In terms of the cost-benefit ratio for the use of low-dose, incisive neuroleptics, important benefits did appear to accrue from treatment. First, reduction in hyperactivity and autistic-like behaviors was associated with improved peer interactions. Second, enhanced cognitive organization and diminution in the excessive preoccupation with fantasies rendered the children more amenable to psychotherapeutic and behavioral interventions. Finally, the behavioral improvements in seven of the 12 patients were of such a magnitude as to allow them to return to their homes for outpatient management instead of being committed to long-term residential care. Nevertheless, intervention with neuroleptics does raise the risk for the development of tardive dyskinesia, a potentially irreversible neurologic side effect (12). Furthermore, it is unclear whether behavioral and cognitive improvements will be sustained following withdrawal of neuroleptics after long-term treatment. In four of the 12 patients, cessation of neuroleptic treatment after 2–7 weeks of administration resulted in recurrence of all symptoms. Since the risk of tardive dyskinesia increases with duration of treatment, the implications of long-term management of neuroleptic-responsive children with pervasive developmental disorder need to be assessed. Objective evidence of the therapeutic effects of this pharmacological intervention in pervasive developmental disorder requires a double-blind, placebo-controlled study.

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Carbamazepine and Hyponatremia in Patients With Affective Disorder

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The authors assessed 20 carbamazepine-treated patients for the development of hyponatremia. None of the patients had readings below 135 meq/liter of sodium before carbamazepine therapy, but five (25%) did have such readings after carbamazepine therapy. Three of these patients developed frank symptoms of hyponatremia within 1–3 months of the start of therapy. In one patient, hyponatremia developed after rechallenge with carbamazepine. The authors suggest that caution be used in prescribing carbamazepine to patients with low or borderline low sodium values.

(Am J Psychiatry 1988; 145:339–342)

Carbamazepine, an iminodibenzyl anticonvulsant, is effective in several neuropsychiatric disorders, including psychomotor epilepsy (1), trigeminal neuralgia (2), aggressive behavior in psychiatric patients (3–5), and affective disorders (6–10).

Several side effects, however, have been reported with carbamazepine (11–13). Hyponatremia was found to be common in patients with epilepsy and those with trigeminal neuralgia (14–17). This side effect has been used effectively in the treatment of diabetes insipidus (18) but with mixed results in lithium-induced nephrogenic diabetes insipidus (19, 20). Few studies, however, have been conducted on the prevalence of hyponatremia in patients with affective disorder. Two studies (21, 22) and two case reports (23, 24) have indicated that this side effect may also occur in patients with affective disorder.

We assessed the prevalence of hyponatremia in the course of carbamazepine therapy in 20 patients with affective disorder in our hospital.

METHOD

A total of 20 patients (10 men, 10 women) were assessed for the development of hyponatremia following carbamazepine therapy in the inpatient services of Douglas Hospital Centre, Québec, Canada. Each patient underwent three baseline evaluations for the cations sodium and potassium and the anion chloride. The evaluations were made 1 week apart. The electrolyte values were determined by the SMAC-12 automated technique. The normal values in our hospital are 135–145 meq/liter for sodium, 3.5–5.0 meq/liter for potassium, and 98–108 meq/liter for chloride. Following carbamazepine therapy, the same tests were repeated once a week for 1 month and once every 2 weeks for the continuation of the observation period. In addition, carbamazepine plasma levels were ascertained with each electrolyte evaluation by using enzyme immunoassays (normal range=6–12 μg/ml).

Of the 20 patients, 18 were diagnosed as suffering from bipolar I disorder and one each had bipolar II and unipolar depression. The criteria for diagnosis followed *DSM-III*. None of these patients had a previous history of self- or drug-induced water intoxication. All 20 patients had normal sodium values before carbamazepine therapy.

The mean±SD age of the patient population was 61±11.4 years. The mean±SD duration of carbamazepine treatment was 18.1±15.8 months. The mean±SD dose of carbamazepine was 695±287.7 mg/day. Three of the patients were also receiving lithium carbonate (doses varied from 300 to 900 mg/day), four were receiving antidepressants (doxepin, 100 mg/day, in three patients and trazodone, 75 mg/day, in the fourth), and four were receiving neuroleptics (thioridazine, 200 mg/day, in one patient; chlorpromazine, 600 mg/day, in two patients; and trifluoperazine, 30 mg/day, in the fourth). Nine patients received carbamazepine alone. None of the patients received concurrent diuretic medication because this has been found to increase the chances of developing hyponatremia (25).

RESULTS

All 20 patients had normal electrolyte levels before treatment. After carbamazepine treatment was initiated, the electrolyte levels of 15 patients remained unchanged, but the sodium concentrations of five (25%) of the patients decreased substantially. The mean sodium levels in the 15 patients whose electro-

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TABLE 1. Electrolyte Values of Five Patients With Affective Disorder Who Developed Hyponatremia After Carbamazepine Treatment

Patient and Time	Age (years)	Sex	Carbamazepine Plasma Level (µg/ml)		Electrolyte Value (meq/liter)					
					Sodium		Potassium		Chloride	
			Mean	Range	Mean	Range	Mean	Range	Mean	Range
Patient 1	50	F	7.0	4.7–8.6						
Before carbamazepine treatment					138	135–140	4.3	4.2–4.4	106	105–107
After carbamazepine treatment					131	128–133	4.5	4.4–4.6	97	96–97
Patient 2	64	F	5.0	3.9–6.7						
Before carbamazepine treatment					141	137–142	3.7	3.5–4.0	98	90–100
After carbamazepine treatment					132	128–136	3.5	3.3–3.7	97	88-104
Patient 3	32	F	7.0	6.6–7.5						
Before carbamazepine treatment					140	138–143	4.2	4.0–4.5	109	107–111
After carbamazepine treatment					127	125–128	4.3	3.8–4.8	94	90–97
After carbamazepine discontinuation[a]					140	137–141	4.2	4.0–4.4	108	106–110
Patient 4	53	F	6.0	4.1–9.2						
Before carbamazepine treatment					138	135–139	4.5	4.4–4.6	101	101–103
After carbamazepine treatment					128	126–129	4.4	4.1–4.6	88	87–88
After carbamazepine discontinuation					138	135–139	4.3	4.0–4.5	103	100–105
Patient 5	75	M	5.0	3.8–5.7						
Before carbamazepine treatment					136	135–137	4.7	4.1–5.2	96	88–100
After carbamazepine treatment					126	124–128	4.2	4.0–4.4	91	90–92
After carbamazepine discontinuation					140	138–142	4.9	4.5–5.2	106	100–110

[a] Patient developed hyponatremia on rechallenge.

lyte levels did not change were 140 ± 1.4 and 140 ± 1.9 meq/liter, respectively, before and after carbamazepine treatment (ranges=137–146 and 135–145). The mean potassium levels for these patients were 4.2 ± 0.3 and 4.3 ± 0.2 meq/liter (ranges=4.0–5.0 and 3.8–4.5), respectively, and their mean chloride levels were 104.0 ± 2.4 and 104.1 ± 2.5 meq/liter (ranges=97–107 and 98–108). The mean carbamazepine plasma level of these 15 patients was 6.8 ± 1.5 µg/ml.

Of the five patients (one man, four women) who developed sodium levels lower than 135 meq/liter during carbamazepine treatment, three had hyponatremic symptoms. The electrolyte values for all five patients who developed hyponatremia are shown in table 1.

Patients 1 and 2 developed asymptomatic hyponatremia (sodium values less than 135 meq/liter) within the first 3 months of initiating carbamazepine therapy. Their sodium levels returned to normal, so carbamazepine treatment was continued. Patient 1 received thioridazine, 200 mg/day, and patient 2 received chlorpromazine, 600 mg/day, during the study period.

Patients 3, 4, and 5 developed frank symptoms of hyponatremia. These included excessive water drinking in all three patients as well as lethargy, tiredness, and fatigue in patients 4 and 5. None developed epileptic seizures. Patient 3 was also receiving chlorpromazine, 600 mg/day, and patient 4 was receiving trifluoperazine, 30 mg/day, in addition to carbamazepine. Patient 5 received only carbamazepine.

Upon discontinuation of carbamazepine in patients 3, 4, and 5, sodium values returned to pretreatment levels within 1 month. Patient 3 developed hyponatremia on rechallenge 8 months later. Medication other than carbamazepine was still continued after carbamazepine discontinuation.

Chloride levels decreased along with sodium values and returned to normal after carbamazepine was discontinued. The potassium levels of all 20 patients were not affected during the study period.

As seen in table 1, the mean carbamazepine plasma levels were in the lower therapeutic range of our laboratory.

DISCUSSION

In this study carbamazepine caused a reduction of sodium and chloride levels in five (25%) of 20 patients and caused symptomatic hyponatremia in three of the 20 patients. This high prevalence of hyponatremia confirms previous studies in neurological patients (14–17). In these studies, the prevalence of hyponatremia due to carbamazepine varied from 15% to 23%. Few studies have been conducted of patients with affective disorder to determine the prevalence of this side effect. A preliminary study of 12 patients (21), later extended to a total of 44 patients (22), most of whom were diagnosed as suffering from affective disorder, found that carbamazepine caused statistically significant but clinically insubstantial reductions in serum sodium and calcium but not in magnesium and potassium. Symptomatic hyponatremia was present in two of 44 patients, and sodium levels decreased in 20 other patients. None of the patients was receiving any other medication besides carbamazepine. Two subsequent papers (23, 24), involving three patients, indicated that hyponatremia can occur in patients with affective disorder in the course of carbamazepine therapy. Thus, reduction in serum sodium is a pharmacological effect of carbamazepine independent of the underlying diagnosis.

Uhde and Post (21) suggested that hyponatremia as a side effect of carbamazepine developed more readily in patients who had the lowest pretreatment sodium levels. This was evident in our patient 5 (table 1), whose mean sodium level before carbamazepine therapy was 136 meq/liter (low normal for our laboratory). Thus, caution should be observed in patients who have low sodium values when starting carbamazepine therapy.

The relationship between carbamazepine plasma level and hyponatremia is difficult to assess in our patient population because carbamazepine levels fluctuated from one day to another on the same dose schedule in a given patient. Other studies of patients with affective disorder (21, 22) and epilepsy (13) found that carbamazepine plasma levels were not a dependable therapeutic gauge of response or side effects.

Hyponatremia in psychiatric patients can be caused by psychosis (26), compulsive water drinking (27), or different psychotropic drugs (28). Because four of our five patients who developed hyponatremia were also receiving neuroleptics, the possibility exists that the combination of neuroleptics and carbamazepine may have led to the development of hyponatremia. However, these patients had been receiving neuroleptics for many years before carbamazepine therapy was started and did not have a history of water intoxication or sodium levels below the norms of our laboratory. Also, when carbamazepine was discontinued, sodium levels returned to baseline, despite the continuation of the neuroleptic treatment. In addition, patient 3 developed hyponatremia on rechallenge with carbamazepine but again returned to normal after carbamazepine was discontinued.

Several studies have been conducted to understand the mechanism of hyponatremia due to carbamazepine. This medication was found to raise the secretion and/or synthesis of vasopressin from the hypothalamus (29), and it has been hypothesized (30) that carbamazepine might raise renal sensitivity to normal plasma vasopressin concentrations, resetting the osmoreceptors so that they become "lazy." Gold et al. (31), studying eight patients with affective disorder and comparing them with control subjects, found that carbamazepine lowered the plasma vasopressin response to hypertonic saline in the patients, presumably by enhancing renal responsiveness to vasopressin. In a previous study (32), they were able to demonstrate that lithium carbonate had an opposite effect to carbamazepine on vasopressin.

In conclusion, hyponatremia secondary to carbamazepine therapy was found in 25% of our study group. It occurs most commonly in the first 3 months of carbamazepine therapy. Caution should be used when prescribing carbamazepine for patients who have borderline low sodium values. Hyponatremia is reversible after carbamazepine discontinuation.

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Association of Low Serum Anticholinergic Levels and Cognitive Impairment in Elderly Presurgical Patients

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Low-dose scopolamine, given as presurgery medication, resulted in low levels of serum anticholinergic activity and caused measurable cognitive impairment in 18 psychiatrically healthy elderly patients. The degree of impairment was directly related to serum anticholinergic activity levels and, in the small subgroup of patients scheduled for spinal anesthesia, to CSF anticholinergic activity. Two of the mental status tests used, the Rey Auditory-Verbal Learning Test and the Saskatoon Delirium Checklist, were sensitive enough to detect these mild drug-induced changes, while two other tests, the Mini-Mental State and the Symbol Digit Modalities Test, were not.

(Am J Psychiatry 1988; 145:342–345)

Psychiatric patients frequently receive medications with potent anticholinergic effects. Cognitive impairment (1), particularly in the elderly (2), is a common manifestation of the anticholinergic property of many drugs. Several reports have shown a correlation between reduced cognitive function and serum anticholinergic activity (3–6), but these studies did not use a double-blind design and their conclusions have been confounded by the use of subjects with other causes of cognitive impairment such as schizophrenia, ECT, multiple medications, or cardiovascular abnormalities. In the present study we evaluated the hypothesis that low levels of serum anticholinergic activity produced by a small dose of scopolamine would induce mild cognitive impairment rather than frank delirium in normal elderly individuals. We used a group of elderly, psychiatrically healthy, presurgical patients and eliminated some of the design problems inherent in the previous reports. We also compared the sensitivity and clinical utility of several cognitive function tests in detecting early or mild anticholinergic toxicity.

METHOD

Informed consent was obtained from 36 inpatients at the University Hospital, Saskatoon, who were scheduled for noncranial neurosurgery or for general, urologic, or orthopedic surgery and who were 59 years old or older. Patients were excluded if they were scheduled for cardiovascular or thoracic surgery or craniotomy, received regular psychotropic medication, or had psychiatric disorders, language or sensory difficulties, or medical contraindications to anticholinergic medications. In general, consecutively admitted patients were selected, except that priority was given to patients scheduled for spinal anesthesia. The patients' ages ranged from 59 to 81 years (mean ± SD=67 ± 5.9), and their mean educational level was 9.5 ± 2.6 years. There were 22 men and 14 women in our sample.

On the evening before surgery, all participants were given our mental status battery and 10 ml of blood was collected. Subjects were randomly chosen to receive

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TABLE 1. Postinjection Anticholinergic Levels and Cognitive Function Test Scores for Elderly Patients Receiving Placebo or Scopolamine

	Placebo Group			Scopolamine Group			
		Value			Value		
Variable	N	Mean	SD	N	Mean	SD	Significance[a]
Anticholinergic activity (pmol/ml of atropine equivalent)							
Serum	16	11.6	18.2	14	121.1	85.5	F=19.90, df=1, 27, p<0.0001
CSF	4	0.0	0.0	5	74.2	44.8	t=3.31, df=7, p=0.01
Delirium checklist score[b]	17	37.0	2.7	16	33.3	4.1	F=5.99, df=1, 30, p=0.02
Mini-Mental State score[b]							
Total	16	28.3	2.2	16	26.7	3.5	n.s.
Serial sevens	16	4.4	0.7	16	3.6	1.8	n.s.
Symbol Digit Modalities Test score[b]	17	36.0	12.1	16	28.4	13.3	n.s.

[a] Significance levels were derived from analyses of covariance with preinjection measures as covariables, except for CSF anticholinergic activity, which was derived from a t test for independent samples.

[b] A higher score indicates superior performance.

intramuscular injections of placebo or 0.005 mg/kg of scopolamine, a drug formerly widely used as an anticholinergic surgical premedication, 2 hours before surgery. The one patient in the drug group who was over 80 years old received 0.0025 mg/kg of scopolamine. The investigators, ward staff, and patients were blind to the drug/placebo condition of the subjects. The mental status battery was repeated 45 minutes to 1 hour after the presurgery injection. All mental status testing was done by the same investigator. At induction of anesthesia, a second 10-ml blood sample was taken, as was 2 ml of CSF, from the nine patients receiving spinal anesthesia. Anticholinergic activity in serum and CSF was measured by a modification of the competitive radioligand binding assay of Tune and Coyle (7) and is expressed in atropine equivalents as the concentration of atropine giving comparable inhibition of ligand binding to a known concentration of muscarinic receptors.

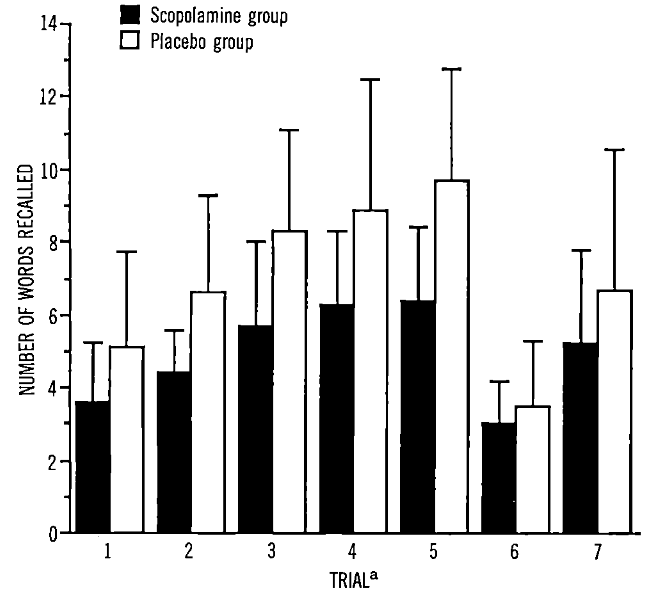
The mental status battery included the Mini-Mental State examination (8); the Saskatoon Delirium Checklist, developed by us from the *DSM-III* criteria for delirium to give a numerical rating score (40=unimpaired and 0=maximal delirium) (see appendix 1); the Symbol Digit Modalities Test (9), a timed visual-motor performance test; and the Rey Auditory-Verbal Learning Test (10, pp. 422–429). In all four tests, the lower a patient's score, the greater the impairment. The Rey Auditory-Verbal Learning Test is a word learning task in which a list of 15 common, unrelated nouns is read to the patient five times and the patient recalls in any order as many of the words as possible after each reading. A recall trial of a distractor list of 15 other nouns follows the fifth trial. Finally, the patient is asked to recall the words from the original list. The patient is scored on the number of correct words recalled on each trial. The entire test battery took about 15 minutes to administer. We did not specifically control for other medications that the patients might be taking. In the 12 hours before surgery, the patients received a mean of 2.2 other drugs, but our groups did not differ in the mean dose of hypnotics or analgesics taken. No recognized anticholinergic drugs were given in the 24 hours before the scopolamine or placebo injections. All data are reported as mean ± standard deviation.

RESULTS

Many patients had measurable serum anticholinergic levels at pretest, with an overall mean of 9.1 ± 17.7 pmol/ml of atropine equivalents. Due to this and to performance differences at the time of predrug testing between the two groups of randomly assigned patients, analyses of covariance were used to determine whether group differences at posttest were significant after the effects of any initial differences between the groups had been eliminated. The mean postinjection anticholinergic levels and cognitive function test scores for patients receiving placebo or scopolamine are given in table 1 and figure 1. Due to assay or procedural accidents, data from all 36 patients were not available for all measures. Subjects receiving scopolamine developed significantly higher serum anticholinergic levels than the control subjects (table 1). In the nine patients scheduled for spinal anesthesia, CSF anticholinergic levels correlated significantly with serum levels (Spearman rank correlation coefficient r_s=.69, p<0.05).

During postdrug testing with the Rey Auditory-Verbal Learning Test (figure 1), the subjects in the scopolamine group recalled fewer words over the five learning trials than did the placebo control group. Although this overall difference was not significant by analysis of covariance, the Groups by Linear Trend interaction (F=3.36, df=1, 30, p<0.10) showed that the difference between the groups tended to increase linearly over the five trials. By the fifth trial, the covariance-adjusted score for the scopolamine group was significantly lower than that for the placebo group (t=2.50, df=31, p<0.01). Drug-induced changes were

FIGURE 1. Mean±SD Number of Words Recalled in the Rey Auditory-Verbal Learning Test by Elderly Patients Receiving Scopolamine or Placebo



^aA recall trial of a distractor list of 15 nouns was given in trial 6, and the original list of 15 nouns was given again in trial 7. An analysis of covariance and a post hoc t test indicated that the two groups were significantly different by trial 5 (t=2.50, df=31, p<0.01).

also detected by the Saskatoon Delirium Checklist but not by the other tests in our battery (table 1).

In addition to the placebo-scopolamine comparisons already discussed, we examined the effects of different serum anticholinergic levels on performance. Using a cutoff criterion of 2 standard deviations above the mean serum anticholinergic level for the overall sample at pretest, we defined groups of patients having "negligible" (below 45 pmol/ml of atropine equivalents) or "low" (45 to 200 pmol/ml of atropine equivalents) serum anticholinergic activity at posttest. Results for these groups were similar to the findings for the original groups. Compared to the negligible group, those with low anticholinergic levels recalled significantly fewer words on trial 5 of the Rey Auditory-Verbal Learning Test (t=2.11, df=25, p<0.025). They also obtained a mean score of 3.2±2.0 (out of a possible score of 5) on the serial sevens item of the Mini-Mental State, compared with 4.4±0.7 for the group with negligible plasma anticholinergic levels (F=5.25, df=1, 24, p<0.05, analysis of covariance). The serial sevens score of the negligible group was the same as that of the placebo group (table 1). There were no differences on the full Mini-Mental State or on other tests or items between the negligible and the low groups.

DISCUSSION

Our results suggest that even low anticholinergic drug levels can cause mild but measurable cognitive impairment in elderly presurgical patients. Earlier studies (3–6) found a correlation between anticholinergic levels and cognitive impairment, but a directly causal relationship could only be assumed. The use of a randomized, double-blind design and analysis of covariance in the present study helps ensure that extraneous sources of variation have been controlled and that the Saskatoon Delirium Checklist scores and the decrement in Rey Auditory-Verbal Learning Test scores are in fact due to elevated serum anticholinergic levels. The particular pattern of verbal learning impairment suggests that scopolamine interferes with the acquisition phase rather than the retrieval phase of memory processing.

Previous studies focused on marked cognitive impairment, involving a mean decline of 2 or more points on the Mini-Mental State (5) or a diagnosis of delirium (3). The important clinical problem of mild or early cognitive impairment due to anticholinergic toxicity has not been previously addressed. Yet it is at this early stage, before the appearance of gross impairment, that preventive intervention is most reasonable. Improved patient management would follow from the use of biochemical and mental status measures that are sensitive to low levels of anticholinergic toxicity. The widely used Mini-Mental State, like many other structured mental status examinations, was designed primarily to document the sort of marked cognitive decline that characterizes frank delirium or dementia (8). It appears to be less useful in detecting mild or transient impairment of the sort that often becomes clinically important in the early phases of drug toxicity, in many elderly patients, and in early dementias.

The results of our study suggest that the Saskatoon Delirium Checklist, the Rey Auditory-Verbal Learning Test, and the determination of serum anticholinergic activity levels may be helpful additions to other diagnostic approaches when early anticholinergic toxicity is suspected. Having baseline data on cognitive function before administration of drugs with anticholinergic activity could also be useful, particularly in sensitive groups such as the elderly. Both the Saskatoon Delirium Checklist and the Rey Auditory-Verbal Learning Test appear to be able to detect the cognitive changes produced by very low levels of anticholinergic activity. At the present time, the Saskatoon Delirium Checklist appears to be a promising clinical research tool. It can be scored after brief observation and, by assignment of numerical ratings to the *DSM-III* criteria for delirium, allows within-subject and between-group comparisons to be made. However, much work in validating and analyzing the delirium checklist remains to be done. The Rey Auditory-Verbal Learning Test, an objective test that can be easily administered in 7–10 minutes, seems to be particularly sensitive to disruption by drugs with anticholinergic actions.

The competitive binding assay provides a means of quantifying anticholinergic activity in samples of various body fluids even after a single dose of a very small amount of scopolamine. This assay measures not only scopolamine but all drugs with affinity for the muscarinic acetylcholine receptor. Since a great many drugs have anticholinergic activity and our data indicate that the higher the serum anticholinergic activity the greater the cognitive impairment, in assessing patients for possible drug-induced cognitive deficits, it is important to know the total serum anticholinergic activity rather than blood levels of any one drug. Although our data do not allow conclusions regarding the neurochemical mechanisms responsible for the scopolamine-induced cognitive impairment, we did find a positive correlation between serum and CSF anticholinergic activity. Consequently, our data are consistent with the hypothesis that anticholinergic drugs impair cognitive function by disrupting neurotransmission at muscarinic acetylcholine receptors in the brain, probably in the hippocampal pathways involved in memory formation. Finally, these findings suggest the need for further development and application of specific mental status tests for conditions with mild or fluctuating cognitive impairment and for continued exploration of the uses of the anticholinergic assay in psychiatry.

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APPENDIX 1. The Saskatoon Delirium Checklist

Please fill out this checklist once prior to preoperative medication and once after preoperative medication but before leaving the floor for surgery.

Approximately how many hours did you observe the patient?
24 12 8 4 2 hours. Other:

Please mark the category that seems most appropriate given your own observations of the patient over the above period. Use your best judgment.

Type of Symptom Observed	How Often Were These Symptoms Observed?				
	Never 4	Very rarely 3	Sometimes 2	Usually 1	Always 0
1. *Reduced* clarity of consciousness: clouding, distractibility	___	___	___	___	___
2. *Perceptual disturbances*: hallucinations, illusions, misinterpretations of real sensations	___	___	___	___	___
3. *Incoherent speech*: impaired language, difficult to communicate effectively	___	___	___	___	___
4. *Sleep disturbance*: impaired sleep/wake cycle, insomnia, daytime drowsiness	___	___	___	___	___
5. *Slowing in motor behavior*: psychomotor retardation, sluggishness	___	___	___	___	___
6. *Agitation*: restlessness, hyperactivity, picking, sudden changes of position	___	___	___	___	___
7. *Disorientation* to person, place, or time	___	___	___	___	___
8. *Other* memory problems	___	___	___	___	___
9. *Fluctuation* of above symptoms over time	___	___	___	___	___ (very rapid changes)

	None 0	Scanty 1	Fair 2	Good 3	Conclusive 4
10. *Physical* cause for symptoms: amount of evidence by history, physical exam, lab, or medications	___	___	___	___	___

(Leave blank if you have any questions about this.)

Date: ________ Time: ________ Signature: ____________________
prior to preoperative medication
after preoperative medication but before leaving the floor for surgery

The Role of Polysomnography in the Differential Diagnosis of Chronic Insomnia

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The authors examined the accuracy of the differential diagnosis of chronic insomnia with and without sleep laboratory studies in a consecutive series of 123 patients. All patients were evaluated by means of a sleep/wake log, a sleep habits questionnaire, structured psychiatric and clinical interviews, and a minimum of two consecutive nights of polysomnography. Notwithstanding a high rate of Research Diagnostic Criteria (RDC)-diagnosed psychopathology (63%) in this sample, the major finding was that in 49% of the patients laboratory results added to, refuted, and/or failed to support the clinical impression. This resulted in substantial modification of the initial diagnostic formulation and therefore in increased specificity of diagnosis.

(Am J Psychiatry 1988; 145:346–349)

As exemplified by deliberations of APA's Work Group to Revise *DSM-III*, the role of sleep laboratory evaluation of patients complaining of chronic insomnia remains a matter of considerable controversy. Although many investigators consider that such laboratory evaluation is necessary for the complete assessment and most specific diagnosis of insomnia, others (noting high rates of *DSM-III*-diagnosable psychopathology in patients with chronic insomnia) believe that the face-to-face office interview is sufficient and that sleep laboratory evaluation is not likely to have a major impact on diagnosis and treatment planning (1, 2).

Although some previous publications have emphasized the heterogeneity of differential diagnostic possibilities (3–5), to our knowledge no systematic examination of the accuracy of differential diagnosis in chronic insomnia with and without polysomnography has been published. Thus, the purpose of this study was to determine the various uses of sleep laboratory evaluation in the diagnosis of chronic insomnia and, more specifically, to ascertain how frequently laboratory findings either add to or fail to support the clinical impression.

METHOD

This was a retrospective study based on a chart review of 123 consecutive patients with chronic insomnia evaluated at the Sleep Evaluation Center of Western Psychiatric Institute and Clinic over a 5-year period (from January 1981 to March 1986). All patients accepted for evaluation had suffered for at least 1 year from inadequate, insufficient, or nonrestorative sleep, and most had not improved with routine interventions (e.g., prescription of sleeping pills).

In all cases, the final diagnosis had been made by using the criteria of the Association of Sleep Disorders Centers (4) for disorders of initiating and maintaining sleep. The final diagnosis reflected the input of the sleep laboratory. The distribution of final diagnoses of disorders of initiating and maintaining sleep for the 123 patients (table 1) is similar to the distribution for chronic insomnia reported by Coleman et al. (3) in their review of 8,000 patients with sleep/wake disorders. Patients had also been initially diagnosed, before polysomnography, by using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (6). Research Diagnostic Criteria (RDC) (7) diagnoses are listed in table 1. Overall, 78 (63%) of the 123 patients were diagnosed as having present or past mental illness. The most frequent RDC diagnoses were affective disorders (40 patients, 33% of the sample) and anxiety disorders (27 patients, 22% of the sample).

All patients in the study had been given a standardized evaluation consisting of an initial interview (including review of sleep logs) and 2 nights of polysomnography. Each patient's final diagnosis and treatment plan had been determined in a consensus conference. No a priori selection had been made with respect to polysomnography (i.e., all patients with chronic insomnia had been given polysomnography).

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TABLE 1. RDC Diagnoses and Association of Sleep Disorders Centers Diagnoses of 123 Patients

Diagnosis	N	%
RDC diagnoses based on SADS-L		
Never mentally ill	45	36.6
Schizophrenia	2	1.6
Bipolar depression	1	0.8
Major depression	16	13.0
Recurrent major depression	10	8.1
Chronic intermittent depression	13	10.6
Panic disorder	2	1.6
Generalized anxiety disorder	25	20.3
Labile personality	3	2.4
Antisocial personality	2	1.6
Alcoholism	1	0.8
Drug abuse	2	1.6
Organic mental syndrome	1	0.8
Final Association of Sleep Disorders Centers diagnoses of disorders of initiating and maintaining sleep		
Associated with affective disorders	36	29.3
Associated with symptom and personality disorders	2	1.6
Persistent psychophysiological	23	18.7
Associated with nocturnal myoclonus	15	12.2
Associated with "restless legs"	4	3.3
Associated with other medical conditions	14	11.4
Associated with sleep apnea	11	8.9
Associated with tolerance to or withdrawal from CNS depressants	8	6.5
Associated with sustained use of or withdrawal from other drugs	1	0.8
Childhood onset	5	4.1
Associated with atypical polysomnographic features	2	1.6
No abnormality; not otherwise specified	1	0.8
No abnormality; subjective complaints without objective findings	1	0.8

The diagnostic interview had been conducted by a psychiatrist polysomnographer (C.F.R.) who formulated an initial clinical impression of the patient's problem based on the patient's self-report; spouse or family report; medical, social, and psychiatric history; a structured psychiatric interview (SADS-L); a sleep habits questionnaire; a 2-week sleep log; and physical examination.

Patients had also kept a sleep log for the 2 weeks before sleep laboratory studies were done and were asked not to take any psychotropic drugs or drink any alcohol during that period; 99 (80%) of the patients were able to comply with that request. Of the remaining 24 (20%) of the patients, 16 (13% of the total sample) were still taking psychoactive drugs, either alone or in combination with alcohol, and eight (7% of the total sample) were still consuming alcohol.

Polysomnography had consisted of a minimum of 2 consecutive nights in the sleep laboratory. In all instances, EEG sleep staging, respiratory monitoring, and at least 1 night of nocturnal myoclonus monitoring had been performed according to procedures specified in Guilleminault's textbook (8). After the scoring of sleep records by a registered polysomnographic technologist, the clinical polysomnographer (C.F.R.) had interpreted the laboratory findings, made a final diagnostic assessment, and formulated treatment recommendations based on both clinical and laboratory findings. The final diagnostic assessments are summarized as Association of Sleep Disorders Centers diagnoses in table 1.

For the purposes of this study, each patient's chart was reviewed by two raters (E.A.J. and A.B.E.) not previously involved in the clinical or laboratory evaluation of the patient. Each rater independently reviewed the three parts of the patient's evaluation in chronological order and made judgments as to whether the laboratory findings 1) confirmed the initial clinical impression, 2) refuted or failed to support it, 3) added new or unsuspected information to it, and/or 4) ruled out a diagnostic possibility.

The confirmation of the initial clinical evaluation by laboratory studies could be achieved in two ways. First, a suspected diagnosis could be confirmed (for example, sleep apnea was suspected clinically and was observed in the laboratory evaluation). Second, laboratory studies could confirm the presence of difficulty in initiating and maintaining sleep but not necessarily identify a more specific finding (for example, nocturnal myoclonus or short REM latency). A laboratory finding was considered to be unsupportive of the clinical impression when the studies did not reveal the presence of a factor believed likely to be contributory. For instance, if the patient, spouse, and family history all suggested nocturnal myoclonus as the main contributory factor but little or no myoclonus was observed in the recording, then a failure to support would be scored by the rater. Sleep studies were rated as adding new information to the clinical impression when something previously not suspected to be a contributory factor was found to be present during polysomnography. Finally, sleep studies were considered to rule out a diagnostic possibility when the interviewer had indicated in the clinical differential diagnosis a need to exclude a particular factor.

These categories are not mutually exclusive: any patient may have met the criteria for one or more of the ratings according to the particular uses of the laboratory for that patient. For example, for one of the patients in this series, a 37-year-old woman who for many years was unable to fall asleep in less than 2 to 3 hours and frequently awakened with nightmares, polysomnography confirmed the clinical suspicion of night terrors, ruled out a possible contribution by sleep apnea, did not support a suspicion of endogenous depression (i.e., REM sleep alterations characteristic of depression were absent), but did reveal the presence of unsuspected nocturnal myoclonus.

To ensure reliability and consistency and to make the findings objective, two raters (E.A.J. and A.B.E.) reviewed and scored each case independently. After all the cases were reviewed, the two independent judgments were compared. If there was a discrepancy between judgments, then the case was reexamined and discussed and a consensus was reached. In most cases the records were reviewed a third time to ensure that the consensus reached among the raters accurately reflected the process of final diagnostic formulation and treatment recommendations.

To facilitate interpretation of the data, we report 95% confidence limits for the major observations, since the latter are expressed as proportional data.

RESULTS

Because of the large number of cases in which there was either a failure to support the clinical impression or a new, unsuspected finding, the diagnoses of 60 (49%) of the 123 patients (95% confidence limit range=40.6%–58.6%) required substantial modification based on laboratory findings. In 50 (41%) of the 123 patients (95% confidence limit range=31.6%–49.6%), laboratory findings provided additional information not previously suspected as important to the patient's chronic insomnia on the basis of clinical evaluation alone. Further, for 24 (20%) of the 123 patients (95% confidence limit range=12.5%–26.5%), laboratory studies failed to support the initial clinical impression. Thus, in a total of 74 instances (60 different patients, or 49% of the sample), laboratory findings failed to support the clinical impression or added to the clinical impression. For 13 (11%) of the patients, studies both added new information and failed to support the clinical impression.

Failure to find EEG sleep alterations characteristic of depression (e.g., REM latency less than 65 minutes) occurred in 17 (71%) of the 24 failures. Nine (38%) of the 24 clinical impressions not supported were due to the failure to confirm sleep apnea, cardiac arrythmias, and nocturnal myoclonus. The 16 patients in whom nocturnal myoclonus was discovered represented the largest percentage of patients with new or unsuspected laboratory findings, accounting for 32% of the 50 patients with new information. Among the other patients with new findings, 13 (26%) were found to sleep better in the laboratory than at home, sleep alterations characteristic of depression were discovered in 10 (20%), and findings of low REM density suggesting the involvement of a neuromedical disorder (i.e., CNS illness) were observed in 13 (26%). The remaining unsuspected laboratory findings were the presence of sleep apnea (N=4), cardiac arrhythmias (N=2), alpha-delta sleep (N=3), delayed sleep phase (N=1), and epileptiform activity (N=1). (More than one new finding applied to some patients.)

For 10 (67%) of the 15 patients with a final diagnosis of disorders of initiating and maintaining sleep associated with nocturnal myoclonus, this diagnosis was new information discovered in the laboratory. Of the 23 patients who were diagnosed as suffering from persistent psychophysiological disorders of initiating and maintaining sleep, nine (39%) were found to sleep better in the laboratory than they reported sleeping at home, supporting the clinical impression that patients have conditioned insomnia in their home environments.

We wondered whether unexpected findings tended to cluster in patients with particular initial diagnostic impressions. This question was approached by comparing the 60 patients with unexpected findings and the 63 patients without such findings. The two subgroups did not differ in age, sex, duration of complaint, specialty of referring physician, or presence of psychopathology. For example, 41 (68%) of the 60 patients with insomnia who did show unexpected laboratory findings had RDC-definable psychopathology, compared with 39 (62%) of the 63 patients without unexpected findings.

DISCUSSION

It is clear that patients with chronic insomnia are likely to have diagnosable psychopathology: two-thirds of the patients in this series had RDC diagnoses, compared with 92% of patients with chronic insomnia who had *DSM-III* axis I diagnoses in the series of Tan et al. (2). However, the main point of the current findings is that, notwithstanding the high rate of diagnosable psychopathology (63%), in 60 (49%) of 123 patients with chronic insomnia referred to a university-based sleep disorders clinic, laboratory findings resulted in a substantial modification of the initial, face-to-face diagnostic formulation.

These unexpected laboratory findings were used in several ways. To take the example of depression, for patients for whom EEG sleep indicators of endogenous depression were absent, treatment recommendations typically accorded priority to nonpharmacological approaches to the patient's insomnia, without, of course, excluding the use of antidepressant chemotherapy if clinically indicated. For other patients, for whom the clinical impression of sleep-disordered breathing was not confirmed, treatment planning would permit the judicious use of benzodiazepines. Similarly, with a new finding of nocturnal myoclonus, treatment planning would specify the use of benzodiazepines to override the sleep-fragmenting effects of nocturnal myoclonus. In the case of patients who slept better in the laboratory than they reported they did at home, treatment would be directed toward behavioral management of the insomnia, such as temporal or stimulus control in the case of psychophysiological or conditional insomnia, rather than pharmacological management. For patients with sleep changes similar to those reported for neuromedical disorders (i.e., greatly diminished REM activity and REM density), recommendations would include a further search for medical disorders known to affect sleep (e.g., endocrinopathy). With laboratory findings of EEG sleep alterations of endogenous depression, the use of tricyclic antidepressant medication would be strongly considered in treatment planning, while if unsuspected sleep apnea were documented, appropriate pulmonary and ear, nose, and throat evaluation would be pursued and CNS-depressant drugs would be contraindicated.

Of course, we are not suggesting that polysomnography should replace the clinician's acumen in the diagnosis and treatment of chronic insomnia or that clinical phenomena be ignored in favor of laboratory findings. Rather, we believe, as others (3, 7) have emphasized, that the differential diagnosis of chronic insomnia is complex and often multiply determined in any given patient and that similar clinical presentations can result from different etiologies. Use of laboratory procedures, therefore, becomes an important adjunct in informed decision making regarding the need for further investigation and/or making specific treatment recommendations. This is in concurrence with the National Institute of Health Consensus Conference on Insomnia in 1983 (5), which recommended that the physician attempt to establish the specific (and possible etiologic) correlates of the patient's complaint of disturbed, inadequate, or excessive sleep with the goal of formulating specific intervention. This does not necessarily mean that full laboratory polysomnography ensures treatment outcome superior to treatment formulated by clinical assessment alone. Clinical research in this area is still sorely needed.

In this context, the conclusions that can be drawn from the current study must be qualified by the absence of a control group. Because this study was a retrospective chart review, a suitable control group was not readily available. Further, because the crucial issue (i.e., do laboratory studies contribute substantially to improved quality of sleep?) can be addressed only in a prospective study, the most appropriate control group would consist of patients with chronic insomnia evaluated and treated without the benefit of laboratory evaluation. In this fashion the issue of whether laboratory evaluation makes a real difference in clinical outcome could be assessed definitively.

Nevertheless, the current data suggest that laboratory studies are useful in making a differential diagnosis and thus a specific treatment plan for patients suffering from chronic insomnia. It has been found that persistent psychophysiological insomnia and insomnia related to psychiatric disorders account for only one-third to one-half of patients complaining of chronic insomnia (3) and must therefore be distinguished from insomnia related to physical conditions, medication use, and other physical conditions that are symptomatic only during sleep and can be diagnosed only during sleep (e.g., sleep apnea and nocturnal myoclonus). A substantial percentage of patients with chronic insomnia (15%–20%) falls into this latter category of disorders of initiating and maintaining sleep associated with sleep apnea and nocturnal myoclonus, and in almost 70% of the patients in our study group who had disorders of initiating and maintaining sleep associated with nocturnal myoclonus, the myoclonus was a new, clinically unsuspected finding of laboratory studies. Taken together, these findings suggest that if one fails to do laboratory studies of patients complaining of chronic insomnia, there is a considerable decrease in overall diagnostic accuracy and confidence.

At this stage, we suggest the following guidelines for deciding whether to order sleep laboratory studies for patients with chronic insomnia. Given the high rate of unexpected laboratory findings (49%) in our sample (as well as the difficulty in predicting which patients will show them), we suggest that polysomnography is indicated for patients with insomnia who have been treatment resistant—i.e., have failed to respond to "routine" clinical interventions. These interventions include attention to "sleep hygiene" issues (e.g., regularity of sleep/wake schedule), sleeping pill detoxification, removal of factors that destroy sleep (e.g., self-medication with caffeine or alcohol), and appropriate psychotherapeutic, behavioral, or pharmacological management of behavioral or psychiatric disorders known to be associated with insomnia.

In this same context, with the particular example involving depression, an unresolved issue is whether unexpected positive or negative laboratory findings reflect poor sensitivity and specificity of EEG sleep measures. Further treatment research is needed to ascertain whether the presence of short REM latency (i.e., less than 65 minutes) specifically indicates that a better treatment response is likely with pharmacological therapy than with specific forms of psychotherapy.

At this time, it is apparent that chronic insomnia can be associated with several factors, often in interaction. The current data suggest that it is useful clinically and scientifically to integrate laboratory measurement with clinical data to clarify the diagnostic heterogeneity which underlies the patient's complaint of insomnia. This in turn will make treatment planning easier, more specific, and, we hope, more efficacious.

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Idiopathic Basal Ganglia Calcification and Organic Mood Disorder

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Idiopathic basal ganglia calcification is a syndrome consisting of bilateral basal ganglia calcifications, neuropsychiatric abnormalities, disturbances of movement, and normal calcium and phosphorus metabolism. The best described neuropsychiatric alterations are dementia and an organic psychosis. Organic mood disorder has been reported less often, and mania secondary to idiopathic basal ganglia calcification has not been noted previously. The authors describe five patients with idiopathic basal ganglia calcification and organic mood changes, including one patient with secondary mania. Symptoms of idiopathic basal ganglia calcification resemble those of other disorders affecting subcortical structures and support an association between mood, affect, cognition, and the extrapyramidal nuclear system. Treatment may ameliorate the mood disorder.

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Idiopathic basal ganglia calcification is a rare disorder of unknown etiology that is manifested clinically by neuropsychiatric abnormalities and abnormal involuntary movements. Post-mortem examination reveals perivascular ferrocalcific deposits in the basal ganglia and dentate nuclei of the cerebellum (1, 2). The condition is usually familial and is distinguished from other causes of basal ganglia calcification by normal calcium and phosphorus metabolism (1). Neuropsychiatric disturbances described with idiopathic basal ganglia calcification include dementia and a schizophrenia-like psychosis (2), but there has been little previous attention to mood and affective abnormalities. This report describes five patients with idiopathic basal ganglia calcification and prominent mood disturbances.

CASE REPORTS

Case 1. Mr. A, a 55-year-old right-handed man, was referred for evaluation of a 7-year history of depression, social withdrawal, and memory loss. He had worked productively until cognitive and motoric slowing forced his early retirement 2 years previously. He noted increased daytime sleepiness with occasional delayed sleep onset but no change in weight or appetite. He was irritable and cried easily.

On examination Mr. A was alert, oriented, and cooperative but markedly slowed. His mood was depressed and his affect constricted, but he did not have any suicidal thoughts, delusions, or hallucinations. Results of mental status testing were normal except for diminished memory recall and poor performance of frontal-systems tasks (e.g., copying multiple loops and alternating programs). He was bradykinetic, had greater than usual muscle tone, and turned *en bloc.* Neuropsychologic evaluation revealed a verbal IQ of 80, performance IQ of 74, and full-scale IQ of 77. There was profound motoric and cognitive slowing: he required up to 10 times the usual amount of time to complete the tests.

Computerized axial tomographic (CAT) scanning revealed dense calcification involving basal ganglia and periventricular gray matter structures (figure 1). Laboratory studies, including determination of serum electrolyte, calcium, phosphorus, and parathyroid hormone levels, were normal. The CAT scan of Mr. A's 14-year-old daughter revealed similar intracranial calcifications.

A diagnosis of idiopathic basal ganglia calcification with mild dementia and organic mood disorder, depressed type, was made. Mr. A was treated with imipramine, and his mood as well as his intellectual function improved.

Case 2. Mr. B, a 47-year-old left-handed accountant, was referred for evaluation of a 7-year history of disruptive and inappropriate behavior. Three years before admission he had experienced mild head trauma in an automobile accident; this exacerbated his symptoms. He was fired from his job for chronic tardiness and constant loud talking that disturbed other workers. His personal hygiene deteriorated, and he refused to shower for up to 6 weeks at a time. He became more aggressive, intrusive, and sarcastic; made inappropriate jokes; exhibited a preoccupation with sexual ideation; and had frequent outbursts of anger.

On examination he was alert, attentive, and well oriented and his psychomotor speed was greater than normal. His speech was pressured, his thought was circumstantial, and distractions produced richly detailed chains of associations that were most often erotic. He was easily irritated whenever thwarted and manifested a euphoric affect. His insight and judgment were poor, and his abstractions were concrete. His

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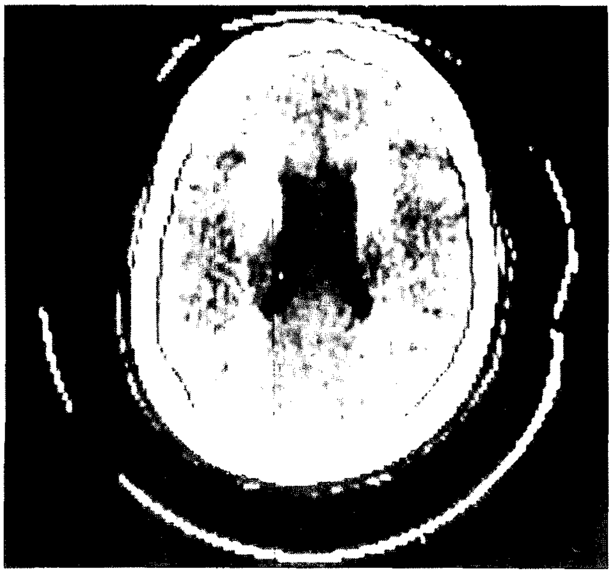
FIGURE 1. CAT Scan of Mr. A[a]



[a]Scan demonstrated dense calcified deposits in basal ganglia and periventricular areas.

language and memory functions were normal, but his frontal-systems functions, constructions, and calculations were impaired. The results of physical examination were notable for marked restlessness, repetitive sucking movements of the mouth, involuntary contractions of the tongue, dystonia of the right hand and shoulder, and slight choreiform movements of the right upper extremity. CAT scan revealed calcification in the basal ganglia, primarily involving the putamen. Routine laboratory studies, including CSF examination and determination of serum calcium and phosphorus levels, were normal. Neuropsychological testing revealed deficits in sustained attention, abstraction, and inhibition of inappropriate responses. A full-scale IQ score of 102 suggested a decline from his previous level of function.

A diagnosis of organic mood disorder, manic type, with idiopathic basal ganglia calcification, was made. Trials of lithium carbonate, 300 mg t.i.d., haloperidol, 5 mg b.i.d., and carbamazepine, 200 mg t.i.d., failed to improve these behaviors. Clonazepam, 2 mg t.i.d., produced some amelioration of his intrusiveness.

Case 3. Mr. C, a 56-year-old right-handed attorney, was admitted after a suicide attempt. His neuropsychiatric history began at age 17 when he was hospitalized for a brief psychotic episode. His behavioral disorder remitted until age 24, when he again developed a schizophrenia-like psychosis. Skull X-rays obtained as part of a neurological evaluation showed dense calcification of the basal ganglia. At age 35 he attempted suicide by ingesting a large quantity of chlorpromazine; he was hospitalized and treated with neuroleptics and ECT. Recurrent psychosis and depression necessitated repeated psychiatric hospitalizations during the next 20 years.

Several family members suffered from undiagnosed neuropsychiatric disorders, and skull X-rays of an aunt revealed calcification of the basal ganglia.

On admission, Mr. C was alert and oriented and his mood was depressed. He had ideas of persecution and intermittent auditory hallucinations. He performed tests of attention, memory, language, calculation, abstraction, construction, and praxis normally but not at the level expected for his educational background. He had prominent buccolingual dyskinesia and choreoathetotic movements of the trunk and neck. His movements were slowed, and his limb tone was greater than usual; he had mild cogwheel-type rigidity. Skull X-rays and CAT scan confirmed the presence of calcification in the putamen, caudate, pulvinar, deep sulci of the frontal cortex, and dentate nuclei. Serum calcium and phosphorus levels and X-rays of carpal and metacarpal bones were normal.

Serial psychological tests performed throughout the course of Mr. C's illness revealed progressive intellectual decline: in high school his IQ had been 167; at 46, his full-scale IQ had declined to 127, and at age 56 it was 120.

Clinical and neuropsychological information suggested a diagnosis of organic delusional syndrome with organic mood disorder and dementia associated with idiopathic basal ganglia calcification.

Case 4. Mr. D, a 56-year-old right-handed machinist, was referred for psychiatric evaluation for feelings of anxiety and suicidal ideation. Since age 47 he had suffered from depression and anxiety. He had been treated with thioridazine, perphenazine, amitriptyline, and diazepam without success. At age 53 he began to exhibit slowing of movements, mild gait ataxia, intermittent bowel and bladder incontinence, occasional drooling, buccolingual dyskinesia, frequent crying episodes, and mild memory loss.

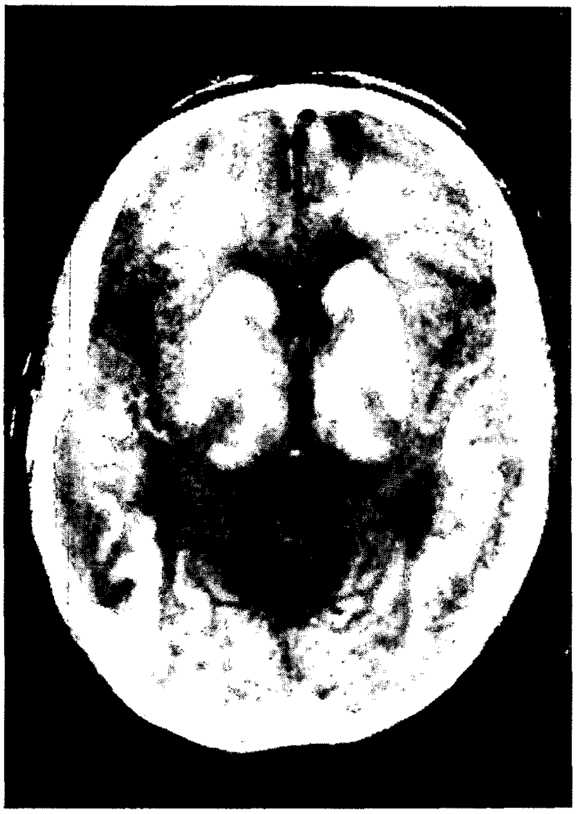
On examination, he appeared slowed but had a full range of affect and manifested no psychotic features. His language and recent memory were normal, but he had deficits of attention and long-term memory. His ability to copy figures was poor. He exhibited tardive dyskinesia and his gait was slow and slightly wide-based.

CAT scan revealed extensive calcification of the basal ganglia, caudate nuclei, thalami, and dentate nuclei of the cerebellum. His electrolyte levels were normal, as were serum and urine calcium and phosphorus, serum magnesium, and thyroid hormone levels. The results of lumbar puncture and EEG were also normal. An MMPI revealed marked paranoid ideation, anxiety, and depression.

A diagnosis of organic mood disorder, depressed type, with features of an organic anxiety syndrome and organic delusional syndrome secondary to idiopathic basal ganglia calcification was made. Trials of alprazolam and oxazepam were not helpful. A trial of L-dopa combined with carbidopa for his psychomotor slowing had equivocally beneficial results but gave him an intense feeling of inner restlessness resembling akathisia. A trial of propranolol made the patient appear less anxious, but he denied any subjective benefit.

Case 5. At the age of 49 Mr. E, a right-handed successful trial lawyer, was rendered unconscious in a robbery attempt. The apparent head trauma was not severe, but a striking deterioration of speech, ataxia, depression, and marked emotional lability were obvious following the incident. Neurological evaluation disclosed no basic abnormalities, but a CAT scan revealed massive intracranial calcification involving the basal ganglia, cerebellum, and areas of the cerebral white matter (figure 2). An endocrine and calcium metabolism workup revealed no abnormalities. His depression slowly abated with antidepressant medication and psychotherapy. The neurological problems also slowly improved,

FIGURE 2. CAT Scan of Mr. E[a]



[a]Scan revealed massive intracranial calcification involving basal ganglia, cerebellum, and cerebral white matter.

but he failed to regain enough function to be able to return to work.

One year after the robbery attempt, Mr. E sustained a minor fall (without head injury) and experienced a recurrence of the severe dysarthria and emotional lability. A movement disorder with parkinsonian features also emerged. Repeat endocrine and metabolic evaluations found no meaningful abnormalities. He again developed a severe depression that responded to psychotherapy. A diagnosis of idiopathic basal ganglia calcification with recurrent depression, emotional lability, and parkinsonism was made.

DISCUSSION

Idiopathic basal ganglia calcification (also called Fahr's disease) is manifested by a syndrome including 1) bilateral basal ganglia calcification, 2) neuropsychiatric abnormalities, 3) extrapyramidal disturbances, and 4) normal calcium and phosphorus metabolism. The disease must be distinguished from other causes of basal ganglia calcification, including hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism, congenital syndromes with cerebral calcification, and calcification following infectious, traumatic, ischemic, neoplastic, vascular, and toxic brain insults (2–9). It is also to be distinguished from calcification of the basal ganglia in normal subjects, where calcium deposits may occur but are of small magnitude and are limited to the region of the globus pallidus (10).

Dementia and a schizophrenia-like psychosis are the best described neuropsychiatric manifestations of idiopathic basal ganglia calcification. The patients reported here draw attention to the association between this disease and organic mood disorder. Each patient had a prominent disturbance of mood in addition to psychosis or anxiety. In four cases, the mood disturbance was of the depressed type, while a fifth had a chronic hypomanic condition.

The mood state of patients with idiopathic basal ganglia calcification has rarely been carefully investigated, but mood disturbances have been noted in a few previously described cases. Francis and Freeman (11) observed that among their patients with idiopathic basal ganglia calcification, one had a depression, two others had affective flattening, and another was apathetic and withdrawn. Sammet and Bucy (12) described a 43-year-old man with idiopathic basal ganglia calcification who had a history of alcohol dependence, Moskowitz et al. (1) reported a patient with the disease who had a 4-year history of depression, and Palubinskas and Davies (6) studied a 30-year-old woman with the disease who had required ECT for treatment of depression. To our knowledge, no previous cases of manic-type organic mood disturbances in association with idiopathic basal ganglia calcification have been reported, but Munir (13) recently described a patient with the disease whose psychotic symptoms responded well to lithium carbonate therapy, suggesting a relationship to secondary mania. In several other cases, lability and irritability were noted, but insufficient information was given to warrant a retrospective neuropsychiatric diagnosis. Konig et al. (14) investigated 62 patients with basal ganglia calcification of all etiologies (idiopathic, hypoparathyroidism, pseudohypoparathyroidism) and found a 52% prevalence of mood disorder.

Organic mood disturbances have been reported in a variety of other disorders involving subcortical structures. Huntington's disease, Wilson's disease, Parkinson's disease, and bilateral subthalamic cerebrovascular infarctions have all been associated with an increased incidence of depression. Likewise, Huntington's disease, Wilson's disease, and postencephalitic parkinsonism as well as a variety of perithalamic acquired structural lesions have produced secondary manic and hypomanic syndromes (15, 16). The common site of involvement in these disorders is the region of the basal ganglia, thalamus, rostral brainstem, and mesodiencephalic junction. Lesions in this area may disrupt monoaminergic projections carrying neurotransmitters that play a role in the mediation of mood and affect (17). In addition, the basal ganglia are themselves important targets of limbic system projections and may be integrally involved in limbic-emotional activity (18–20). Extensive connections between the basal ganglia and the frontal lobe may explain the cognitive and behavioral similarities noted between patients with idiopathic basal ganglia calcification and patients with frontal lobe dysfunction (21). Thus, the structures and neurochemical systems involved in subcortical disorders play key roles in cognition and mood as well as movement, and pathologic involvement results in complex syndromes comprising extrapyramidal motor abnormalities, mood disturbances, and cognitive deterioration.

Treatment of the affective disturbance associated with idiopathic basal ganglia calcification has been attempted with variable results. Of the patients reported here, Mr. A, Mr. C, and Mr. E had some response to treatment of their depression, but Mr. B and Mr. D failed to respond. The response rate of patients with idiopathic basal ganglia calcification may be lower than that of patients with idiopathic affective disorders, but the depression may improve and treatment should be pursued.

Two of the patients described had the onset of their disorder following minor head trauma, and three patients manifested tardive dyskinesia. These observations suggest that the calcification and associated functional disruption may render the patient exceptionally vulnerable to metabolic and traumatic conditions. This vulnerability should be borne in mind when prescribing drugs with extrapyramidal side effects to patients with idiopathic basal ganglia calcification.

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Psychiatric Disorders in Patients With Cerebrotendinous Xanthomatosis

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Cerebrotendinous xanthomatosis is a familial recessive disorder. Patients with the disorder present with tendon xanthomas, juvenile cataracts, dementia, and pyramidal and cerebellar abnormalities but have normal plasma cholesterol. High plasma cholestanol concentrations and abnormal bile acid metabolism are specific for this disease. The authors describe four patients with cerebrotendinous xanthomatosis and prominent psychiatric symptoms. In three of these patients appropriate diagnosis and treatment were delayed for years because the presence of cerebrotendinous xanthomatosis was not recognized. Early recognition of this potentially lethal disease is important because both the psychiatric and neurological symptoms respond to treatment with chenodeoxycholic acid.

(Am J Psychiatry 1988; 145:354–357)

Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder of bile acid synthesis that leads to an accumulation of cholestanol (5α-cholestan-3β-ol) in tissues, plasma, and CSF (1–3). Typically, affected individuals develop tendon xanthomas, cataracts, dementia, pyramidal paresis, cerebellar ataxia, and peripheral neuropathy (1–4). Neurological impairment apparently results from diffuse replacement of cholesterol by cholestanol in the myelin of the central (2, 3) and peripheral nervous systems (5), or, rarely, from the formation of xanthomas in the brain (2–4).

Although clinical recognition of this disorder is usually based on neurological dysfunction, we have recently recognized that psychiatric disorders may also be seen, either as presenting symptoms or during the course of the illness. Because psychiatric manifestations have not been described previously in this disorder, when the patient presents with psychiatric symptoms there may be considerable delay in diagnosis. Early recognition of this slowly progressive and potentially lethal illness is important because the psychiatric and neurological abnormalities respond to treatment with chenodeoxycholic acid (6, 7).

METHOD

We examined 35 patients (23 women and 12 men) with the typical clinical features of cerebrotendinous xanthomatosis including neurological abnormalities, cataracts, and xanthomas (figure 1). All patients demonstrated altered bile acid synthesis (8, 9) and high plasma cholestanol levels. Plasma sterol concentrations were measured by gas liquid chromatography (8). In patients with typical clinical features but cholestanol levels that were only slightly high, diagnosis was confirmed by use of a provocative cholestyramine test. Nine grams of cholestyramine were administered by mouth daily for 1 week, and plasma cholestanol levels were again measured. In individuals with cerebrotendinous xanthomatosis, cholestyramine administration causes a substantial rise in cholestanol levels without a rise in cholesterol, whereas in normal individuals, levels of cholestanol remain essentially unchanged (10). Some of these subjects with cerebrotendinous xanthomatosis have been described in previous reports (1, 11, 12).

We observed prominent psychiatric symptoms in four patients with cerebrotendinous xanthomatosis. Clinical and biochemical data are presented in tables 1 and 2. Neurological findings were those present at the time of psychiatric symptoms. The psychiatric history of each patient is described in the following material.

CASE REPORTS

Case 1. Mr. A, a 43-year-old man, first noted enlargement of his Achilles tendons at the age of 22 years. He was employed until age 32, when he was first hospitalized for a

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FIGURE 1. Typical Achilles Tendon Xanthomas in a 27-Year-Old Man With Cerebrotendinous Xanthomatosis and Psychiatric Disorders (Patient 3)

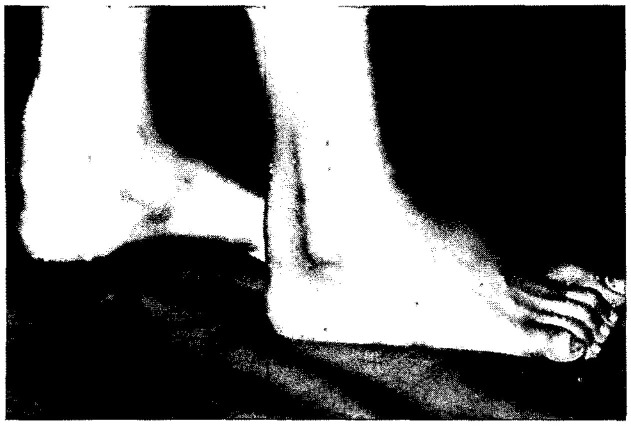

TABLE 1. Clinical Characteristics of Four Patients With Cerebrotendinous Xanthomatosis and Psychiatric Disorders

	Patient			
Characteristic	1	2	3	4
Family history of same disorder	No	Yes	Yes	Yes
Age (years)				
At onset	22	18	12	12
At diagnosis	42	25	22	32
At initial psychiatric symptoms	32	37	27	20
Xanthomas	Yes	Yes	Yes	Yes
Pes cavus	Yes	Yes	Yes	Yes
Cataracts	No	No	Yes	Yes
Neurologic findings				
Dementia	Yes	No	Yes	Yes
Pyramidal signs	Yes	No	Yes	Yes
Cerebellar signs	Yes	No	Yes	Yes
Peripheral neuropathy	Yes	Yes	Yes	—
Brain CAT scan	Mild loss of cortical substance	—	Moderate white matter hypodensity	Diffuse white matter hypodensity
Diffuse slowing on EEG	Yes	Yes	Yes	Yes

TABLE 2. Plasma Sterol Levels in 35 Patients With Cerebrotendinous Xanthomatosis and a Subgroup With Psychiatric Disorders and in 40 Normal Subjects

Group	Cholesterol Level (mg/dl)	Cholestanol Level (mg/dl)
Normal subjects (mean±SD)	221±25	0.2±0.2
All patients with cerebrotendinous xanthomatosis (mean±SD)	215±61	3.2±0.5
With psychiatric disorders[a]		
1	265	1.2
2	200	0.8
3	116	0.8[b]
4	191	3.5

[a] Determinations at time of psychiatric disorders.

[b] Initial level 5 years earlier, before treatment, was 8.8 mg/dl.

personality disturbance characterized by dependency and inappropriate sexual behavior. Since then he had been hospitalized for psychiatric care on six other occasions, with increasing frequency, because of personality changes, irritability, and agitation. Various diagnoses, including schizoaffective disorder and acute dementia praecox, were made. Treatment with phenothiazines provided temporary, limited benefit.

At age 41 years, Mr. A developed auditory hallucinations and paranoid ideation and made a suicidal gesture. Six months later he developed disorientation, slurred speech, poor memory, and ataxia. On examination, he was alert, restless, and dysarthric. His speech was nonsensical and pressured, and the content was inappropriate and silly and included homosexual delusions. He was able to read and name objects but had poor attention and was unable to recall any of five objects 5 minutes after their presentation. Six months later, when he was age 42, his plasma cholesterol level was normal and his plasma cholestanol concentration was slightly high. After a cholestyramine challenge, his plasma cholestanol concentration rose to 3.0 mg/dl. A diagnosis of cerebrotendinous xanthomatosis was made, and therapy with chenodeoxycholic acid was started, at a dose of 250 mg t.i.d. After 6 months of treatment, his neurological status and mentation appeared to improve. His WAIS performance IQ increased from 70 to 77, the verbal IQ from 91 to 93, and the Wechsler Memory Quotient from 93 to 109. The psychiatric problems continued but to a lesser degree.

Case 2. Mr. B, a 38-year-old man, developed Achilles tendon xanthomas at age 16. Similar xanthomas were found later in his sister. He came to medical attention at age 26; at that time his plasma cholesterol level was normal and his cholestanol concentration was borderline. After a cholestyramine challenge, the plasma cholestanol level rose to 3.0 mg/dl. Chenodeoxycholic acid treatment, 750 mg/day, was started, but he took the medication irregularly or not at all. At the age of 37 he developed an atypical psychosis with the persistent delusion that his wife was an imposter. His symptoms resolved while he was treated with haloperidol and chenodeoxycholic acid; haloperidol was discontinued after several weeks.

One year later he stopped taking chenodeoxycholic acid and began talking incoherently, eating poorly, sleeping excessively, and staring persistently. He was inattentive to his surroundings and expressed delusions that he was a cocaine addict and that errors had been made in his paycheck. On examination he appeared anxious, demonstrated poor judgment, and seemed to be responding to internal stimuli, although he denied hallucinations. His symptoms resolved after treatment with haloperidol and chenodeoxycholic acid but recurred 1 month later; at that time he admitted that he had auditory hallucinations. On examination at that time he was alert and oriented but had a flat affect; there was no clinical evidence of dementia. Treatment with chenodeoxycholic acid and haloperidol was continued, with improvement of symptoms over several weeks. He did not exhibit further psychiatric symptoms while receiving only chenodeoxycholic acid.

Case 3. Mr. C, a 27-year-old man, began insidiously developing Achilles tendon xanthomas and progressive dementia at age 12. He was dependent and unable to learn and to work. Cerebrotendinous xanthomatosis was diagnosed at age 22 when a brother was also found to have the disorder. Therapy with chenodeoxycholic acid, 750 mg/day, resulted in reduction of spasticity and ataxia. His mental status improved so that he could carry on a conversation, and he became able to care for himself.

Five years later, despite continued treatment with chenodeoxycholic acid, he experienced the sudden onset of catatonia, possibly reactive, at the time of a family stress. He stopped eating, became incontinent of urine and feces, and was mute, with the exception of a stereotypic phrase that he uttered, blaming his parents for his condition. He was akinetic and mute, had a fixed gaze, and maintained the posture of his arms wherever they were placed. This catatonic episode was treated with haloperidol and chenodeoxycholic acid and lasted about 6 weeks. Afterward, his neurological status was the same as it had been before the catatonia, and it remained stable. Cholestanol levels were normal before and after the catatonic episode.

Case 4. Ms. D, a 36-year-old woman, first developed mental decline, motor retardation, and Achilles tendon xanthomas at the age of 12 years. There was slowly progressive dementia that left her severely impaired, with a WAIS full-scale IQ of 40, by the age of 32. At 22 years of age, she became agitated and aggressive and required many psychiatric hospitalizations to control her behavior. She responded partially to treatment with antipsychotic medications for short periods but continued to be agitated and to exhibit negativistic behavior. At the age of 30 she refused to eat and frequently vomited, to the point of requiring a feeding gastrostomy. Two years later she and her younger sister were diagnosed as having cerebrotendinous xanthomatosis. Her family refused treatment with chenodeoxycholic acid, and her behavior and neurological status continued to deteriorate.

DISCUSSION

These cases demonstrate that psychiatric symptoms may be a prominent manifestation of cerebrotendinous xanthomatosis. In some of our patients, these symptoms developed after neurological improvement had already occurred, and in one case (patient 2), psychiatric symptoms preceded the onset of neurological abnormalities. It is noteworthy that in all of our patients, Achilles tendon xanthomas had developed years before the onset of psychiatric symptoms.

The mechanisms leading to psychiatric disturbance in cerebrotendinous xanthomatosis are unknown. Psychiatric symptoms can develop when neurological signs are stable or improving (patient 3). Furthermore, they can occur in the absence of dementia (patient 2). This suggests that psychiatric symptoms do not simply reflect worsening of dementia in subjects with cerebrotendinous xanthomatosis. The psychiatric manifestations of these patients cannot be classified as a single psychiatric syndrome. Some patients had delusions, hallucinations, paranoid ideation, or catatonia similar to features seen in schizophrenia. In other cases, the psychiatric disturbance was characterized by agitation, aggression, or hyperactivity. It is notable that affective disturbances such as depression were not observed.

Other neurological illnesses that affect CNS myelin may produce prominent psychiatric symptoms. For example, in multiple sclerosis, psychiatric symptoms, most commonly depression, are seen in approximately 60% of patients (13). Psychosis can also be seen in metachromatic leukodystrophy, an inherited metabolic disorder that causes central demyelination (14). These examples illustrate that psychiatric disturbances are produced not only by diseases affecting primarily cell bodies but also by processes affecting primarily neuronal tracts.

Although focal lesions, as well as diffuse pathology, can be seen in cerebrotendinous xanthomatosis, we could make no correlation between focal brain damage and psychiatric symptoms, since none of our patients demonstrated cerebral xanthomas. Our patients did exhibit mild diffuse white matter hypodensity, ventricular enlargement, and widening of sulci on CAT scan (table 1) (11). Although brain stem and cerebellar atrophy on CAT scan may be seen in patients with catatonia (15), no abnormalities of these structures were observed in our patient 3, who developed catatonia. In all our patients, EEG showed diffuse slow activity consistent with metabolic encephalopathy (12).

Long-term treatment with chenodeoxycholic acid is effective in stabilizing and even reversing the neurological deficits caused by cerebrotendinous xanthomatosis (6, 7). However, it remains unclear whether long-term treatment with this drug alone would resolve the psychiatric disturbance in these patients. Extended observations of more patients are necessary. Our observations suggest that with chenodeoxycholic acid treatment, improvement in psychiatric symptoms is likely. The patient who did not receive treatment (patient 4) continued to show both neurological and psychiatric deterioration, in contrast to the three patients who received chenodeoxycholic acid. Symptomatic treatment with psychotropic agents does seem to provide some short-term benefit. Perhaps these patients would benefit most from a combination of chenodeoxycholic acid and antipsychotic medication.

On the basis of these cases, we feel that young patients with atypical psychosis who also have evidence of tendinous xanthomas with or without the other stigmata of cerebrotendinous xanthomatosis warrant measurement of plasma cholestanol levels. In those who have normal cholestanol levels but who are clinically suspected of having cerebrotendinous xanthomatosis, the cholestyramine challenge test can also be used to help establish the diagnosis. Early recognition of this potentially lethal disease is important because both the psychiatric and neurological symptoms respond to treatment with chenodeoxycholic acid.

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Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Oct. 15, 1987, and Jan. 7, 1988.

Donald F. Buckle
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Walter F. Stafford, Jr.
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Prolactin, Cortisol, and Antidepressant Treatment

Giovanni A. Fava, M.D., Jonathan Lisansky, M.D., Maire T. Buckman, M.D.,
Robert Kellner, M.D., Ph.D., Dorothy Pathak, Ph.D.,
Maurizio Fava, M.D., and Glenn T. Peake, M.D.

In four depressed patients with abnormal dexamethasone suppression test results before treatment, plasma prolactin levels significantly increased after successful amitriptyline therapy. Such an increase did not take place in five depressed patients with normal dexamethasone suppression test findings.

(Am J Psychiatry 1988; 145:358–360)

Attempts at establishing a relationship between prolactin and depression have yielded conflicting results. In different comparisons of the basal prolactin levels of depressed patients and normal subjects, the depressed patients' levels have been found to be higher, lower, and the same (1). Similarly, several studies reported that treatment with tricyclic antidepressants significantly raised plasma prolactin levels in depressed patients, yet other investigations failed to detect such an increase (2). In healthy subjects, antidepressants—with the possible exception of clomipramine—were not found to alter plasma prolactin levels (1).

There are several likely reasons for the conflicting results. There have been differences between the samples of depressed patients; some groups were quite heterogeneous. Contaminating variables, such as lack of sleep (3) or periovulatory enhancement and sex steroid modulation of prolactin secretion in women (4), may have also yielded spurious results. Such contaminating effects may be magnified if only random basal levels of prolactin are measured, as in most of the studies. Our group studied prolactin levels determined at 15-minute intervals in depressed patients during illness and after treatment with amitriptyline. Both diurnal (1) and nocturnal (2) prolactin levels were significantly higher after treatment than during acute illness. It was not possible to ascertain, however, whether the observed changes were a consequence of recovery or were a drug effect, a problem already encountered by other investigators in evaluating their results.

Hypothalamic-pituitary-adrenal (HPA) axis disturbances in depression have been extensively substantiated (5). The dexamethasone suppression test (DST), which was originally introduced for the diagnosis of Cushing's syndrome, has been used increasingly as a diagnostic tool for major depression with melancholia (5). In Cushing's disease, hypercortisolism interferes with the regulation of prolactin secretion: nocturnal elevation of the plasma prolactin level is absent (6) and prolactin response to insulin-induced hypoglycemia is blunted (7). Cure of Cushing's disease by selective pituitary adenectomy restores normal prolactin secretion (8).

The purpose of the present study was to examine the influence of cortisol abnormalities on plasma prolactin levels in depressed patients before and after treatment with amitriptyline, after the introduction of procedures likely to reduce some of the biases that may have occurred in previous studies in this area of research.

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TABLE 1. DST Results and Prolactin Levels of Depressed Patients Before and After Amitriptyline Treatment

Patient and Pretreatment DST Response	Age (years)	Sex	Postdexamethasone Cortisol Level (μg/dl)		Plasma Prolactin Level (ng/ml)[a]			
					Before Treatment		After Treatment	
			Before Treatment	After Treatment	Mean	SD	Mean	SD
Nonsuppressors[b]								
1	37	F	6.9	3.5	6.2	1.7	7.2	2.2
2	36	F	5.5	1.6	8.6	2.7	15.2	2.3
3	21	M	9.7	6.5	5.8	1.6	13.5	3.7
4	63	M	7.4	1.4	8.9	1.9	14.0	1.8
Suppressors								
5	36	F	2.6	3.9	6.2	1.8	7.7	2.5
6	26	F	1.6	3.6	12.2	1.2	20.0	3.6
7	35	F	1.8	5.8	10.7	4.1	13.6	6.3
8	36	M	1.9	2.3	7.2	2.7	7.6	2.2
9	21	M	1.6	1.0	5.2	0.3	8.3	2.9

[a] Mean±SD of 21 measurements over 5 hours for each individual.

[b] For nonsuppressors, the mean area under the prolactin level time curve was significantly higher after treatment ($t=3.35$, $df=3$, $p<0.05$).

METHOD

Twelve depressed inpatients, eight women and four men, at the Bernalillo County Mental Health Center in Albuquerque, N.M., gave written consent to participate after the procedures were explained to them. All patients satisfied the *DSM-III-R* criteria for major depression with melancholia and had no physical illnesses. The diagnoses were established by the consensus of two psychiatrists who conducted separate interviews using the Schedule for Affective Disorders and Schizophrenia (SADS). All the female patients were premenopausal. Patients were screened only if during the previous 3 months they had not taken any drug known to affect prolactin and cortisol secretion. All patients had been drug free since at least 15 days before the beginning of the study.

On the first full day of the hospital stay, each patient underwent extensive psychometric evaluation, including Paykel's Clinical Interview for Depression (9). After 4 weeks the patient was rated with the methods used in the first assessment. Only the patients who displayed satisfactory responses to the treatment—according to specific criteria (1, 2)—were included in the study.

Plasma prolactin levels were determined on the second day after admission. For all the women, the studies were done on the same day of the menstrual cycle to minimize the effects of variations in endogenous estrogen secretion on plasma prolactin concentrations. All the studies began within a 30-minute period. The patient was accompanied to the Clinical Research Center of the University of New Mexico between 7:00 and 8:00 a.m. An intravenous catheter was placed in an antecubital vein and kept open with a heparin-saline mixture. During a 30-minute stabilization period, the patient was given a breakfast of his or her choice, which was identical to that served during the second study period. Then 5 cc of blood were drawn into a chilled heparinized tube every 15 minutes for 5 hours, according to the method developed by Buckman et al. (4). Blood was also collected for measurement of plasma estrone, estradiol, progesterone, and 17-hydroxyprogesterone. On the third day of hospitalization, a 1-mg dexamethasone tablet was administered at 11:00 p.m. The next day (day 4), a blood sample for cortisol level determination was obtained at 4:00 p.m. (5).

Each patient was subsequently treated with amitriptyline. The initial dose was 75 mg h.s., which was rapidly increased to 150 mg h.s. The dose was adjusted until the patient reached a satisfactory blood level (150–250 ng/ml). Inpatient treatment lasted about 1 month. After 4 weeks or, for a female subject, on the same day of the menstrual cycle, the patient was tested again for steroid level determination by means of the same methods used in the first assessment. One of the female patients was found to be in a different phase of the menstrual cycle, and sex steroid determinations were not available for two other women. As a result, three female patients were excluded from the analysis.

The blood was stored in ice and centrifuged at 4°C; the plasma was separated and frozen at −20°C until assayed. The levels of plasma prolactin, cortisol, and sex steroids were measured by means of radioimmunoassays, as described in detail elsewhere (1, 2, 4).

Prolactin secretion over time was measured as an integrated area under the curve by using the trapezoid rule (10). Values below 5 ng/ml were converted to 5.0 because of the low reliability of such values. The two-tailed paired Student's t test was used to evaluate differences in integrated prolactin values before and after treatment and between groups. All results are expressed as means and standard deviations.

RESULTS

The five female patients and the four male patients were subdivided according to their DST responses before treatment. Table 1 depicts the endocrine profiles of the patients, who were classified as nonsuppressors (postdexamethasone cortisol levels exceeding 5 µg/dl) or suppressors (below 5 µg/dl). There were no significant differences in the areas under the prolactin level time curves of the nonsuppressors and suppressors either before or after recovery from depression. There were also no significant differences between the nonsuppressors and suppressors in the severity of sleep disturbances, psychomotor agitation/retardation, or weight loss (as measured by Paykel's Clinical Interview for Depression) or in amitriptyline blood levels. The depressed patients who had failed to suppress cortisol after dexamethasone administration, however, showed a significant increase in the mean area under the prolactin level curve after recovery (from 147.4±30.2 to 248.8±71.9 ng/ml per hour; $t=3.35$, $df=3$, $p<0.05$). The difference was not significant in the suppressors (from 150.5±54.6 to 202.0±110.7 ng/ml per hour).

DISCUSSION

These preliminary results, which should be interpreted with caution because of the small sample size, indicate that prolactin secretion increases upon recovery from depression. The prolactin values increased in each of our patients, even though they were always within the normal range. The extent of the increase, however, differed according to DST response before treatment. The increase in prolactin did not appear to be a drug effect or a simple consequence of recovery, since either explanation alone could not account for the difference in the extent of the changes between the suppressors and nonsuppressors.

There is growing knowledge on the interactions between the pituitary-adrenal axis and other endocrine systems, such as those regulating thyroid and growth hormone release, in affective disorders. Our findings underscore the importance of the relationship of cortisol to prolactin in depression. There is both preclinical and clinical evidence that corticosteroids inhibit prolactin release from the pituitary (2). Our findings indicate that the rise in prolactin levels in patients with abnormal DST results appears to be associated with a return to normal of increased HPA axis activity in depression. Whether this is due to the correction of suprapituitary dysfunction that leads to both prolactin and cortisol abnormalities or to the removal of hypercortisolemia, which affects prolactin secretion on a peripheral level, cannot be established by this preliminary study. Mendlewicz et al. (3), studying the 24-hour profile of prolactin in depression, found that the nocturnal rise in prolactin was absent or reduced in several depressed patients, a well-established phenomenon in Cushing's disease (6). In an independent study (2), we found that nocturnal prolactin secretion increased after recovery from melancholia, whereas cortisol secretion decreased. The results of this investigation suggest that studies on prolactin in depressive disorders need to be supplemented by dynamic exploration of HPA axis function.

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Carbamazepine in the Treatment of Catatonia

Heinrich W. Rankel, M.D., and Leonor E. Rankel, M.D.

Carbamazepine resolved within 6–24 hours the catatonic stupor in two patients, one with a schizophreniform and one with a schizoaffective disorder. Reports of frequent EEG abnormalities and the successful use of diazepam in catatonia prompted these trials with another anticonvulsant.

(Am J Psychiatry 1988; 145:361–362)

Catatonic stupor, a condition with multiple etiologies (1), is most frequently accompanied by mutism, rigidity, negativism, posturing, and staring into space (2). The high risk of complications such as deep vein thrombosis and pneumonia warrants a speedy workup and initiation of treatment. Neuroleptic medications act slowly, if at all, and they carry the risk of inducing a neuroleptic malignant syndrome (3). The introduction of benzodiazepines in the management of catatonia (4, 5) has been a breakthrough. Benzodiazepines are, however, usually ineffective in treating the primary condition, and they have a depressant effect on the respiratory system.

To our knowledge, the treatment of a catatonic stupor with carbamazepine has thus far not been reported. Carbamazepine is mainly used as an anticonvulsant but has found entry into psychopharmacology as a lithium substitute (6). The idea of using carbamazepine, an anticonvulsant agent, in the treatment of catatonia came from observations of the striking resemblance of the actions of diazepam in treating both a catatonic state and a status epilepticus. Furthermore, several authors have pointed out that some catatonic patients have abnormal EEGs that are most reminiscent of those in epilepsy (7). We report here on two patients, one with the diagnosis of acute schizophreniform disorder, catatonic type, and the other with the diagnosis of schizoaffective disorder with a catatonic stupor.

CASE REPORTS

Case 1. Ms. A, a 26-year-old woman, was admitted for the first time to the psychiatric department of our hospital. Two days before admission, she had suddenly stopped eating and talking and had remained motionless in bed. At admission she was very rigid and did not respond to verbal or tactile stimuli. She kept her eyes closed and resisted any attempt by the examiner to open them. She also resisted passive movements of her extremities and maintained them in whatever position they were placed. Results of a neurological examination, routine laboratory tests, an EEG, and a CAT scan were all within normal limits.

Ms. A was started on a regimen of carbamazepine, 200 mg t.i.d. Since she refused any food intake, the medication and fluids were given by means of a nasogastric tube. By the end of the first day, the patient was speaking a few words and was being spoon-fed. Her rigidity disappeared. The second day she expressed delusional ideas that her mind was controlled by an outside force. She admitted hearing voices talking to each other but could not specify what they said. We increased the carbamazepine to 200 mg q.i.d., but her psychotic symptoms remained unchanged during the first week. We therefore added 5 mg/day of haloperidol to her regimen. After the second week, her delusions and hallucinations disappeared, and she felt better except for having occasional nightmares. Three weeks after admission Ms. A was discharged in stable condition.

Case 2. Ms. B, a 55-year-old woman, was admitted to our hospital for the third time within a period of 17 years. Her previous diagnoses were endogenous depression and schizophrenia, catatonic type. During her first two admissions she had responded poorly to drugs and therefore had received a series of ECTs. Two weeks before her third admission, she became anxious, depressed, and confused. She thought that she was going to die and asked for a priest. She accused herself of wrongdoing and feared that she would be poisoned. At times her stream of thoughts was incoherent; at other times she just stared at someone. At admission Ms. B appeared anxious and tense and resisted passive movements of her extremities. No verbal communication was possible, and she refused food intake. Results of a neurological examination, an EEG, and laboratory tests were normal.

Ms. B was given an initial 400-mg dose of carbamazepine; a nurse was able to make her swallow the tablet. Thereafter her dose of carbamazepine was 200 mg t.i.d. After 6 hours the patient could be spoon-fed, and she said a few words. On the second day of her hospitalization she was able to eat by herself and to talk. She stated that she was hearing voices giving her orders. She also heard her grandchildren crying, even though they were not present. Suddenly, she got out of bed, knelt on the floor, and prayed. On the third day she stated that she felt a lot better; the voices and her anxieties were almost gone. After 1 week, she had residual paranoid tendencies and hallucinatory experiences, which prompted us to add haloperidol, 1 mg b.i.d., to her regimen. After 2 weeks Ms. B was discharged. She was free of psychotic

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symptoms, and her subjective feeling of well-being was excellent.

DISCUSSION

Carbamazepine, an anticonvulsive agent, was successfully used in the resolution of a catatonic stupor in two patients with the diagnoses of schizophreniform disorder and schizoaffective disorder. No other drugs were administered before carbamazepine was given and until the catatonic stupor had been resolved. Carbamazepine was our first choice for treatment because of our previous success with its use in catatonic patients who were unresponsive to neuroleptic drugs. In addition to the resolution of the stupor, carbamazepine markedly reduced psychotic symptoms such as mannerisms, delusions, and hallucinations in the patient in case 2. In case 1, it seemed to have reduced the amount of neuroleptics needed for the control of the patient's psychotic symptoms, an observation already made by other authors as well (8).

Spontaneous resolution of a catatonic stupor, although rare, does occur. With a fluctuating course of illness such as that in case 2, this possibility cannot be excluded. However, before admission the patient's condition had deteriorated. During previous hospitalizations she had always required ECT, and her lengths of stay had been 6 and 12 weeks; it was only 2 weeks when she was treated with carbamazepine.

The mechanism of action of carbamazepine is largely unknown. It does not act by blocking dopaminergic receptors (9), and it decreases rather than increases turnover of γ-aminobutyric acid (6). It has been suggested that it might suppress a potential subcortical limbic focus and retard the spread of abnormalities to other brain regions (6), a notion that we favor in view of our concept of anticonvulsive therapy in catatonia.

Carbamazepine has no depressant effect on the respiratory system, which is important for patients who develop pneumonia or have other respiratory problems. Except for occasional dizziness, carbamazepine in the therapeutic dosage range usually has no negative effect on mental alertness. Since there is no parenteral form of application available, a nasogastric tube may initially be required.

If schizophrenic or depressive symptoms persist after the catatonic stupor has resolved, neuroleptic or antidepressive therapy should be added accordingly. If carbamazepine fails to relieve a life-threatening catatonic immobility, ECT should be considered.

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Characteristics of Psychiatric Consultations in a Pediatric Cancer Center

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Data on psychiatric consultations with 58 pediatric cancer patients are summarized. Although most patients received DSM-III *axis I diagnoses, adjustment disorder was diagnosed in 30 cases (52%). The patients with primarily depressive features were significantly older than those with anxious features.*
(Am J Psychiatry 1988; 145:363–364)

Despite recent advances in the treatment of pediatric cancers, children with malignancies remain at considerable risk for psychological dysfunction (1–4). Comprehensive cancer centers increasingly rely on psychiatric consultation-liaison services for the diagnosis and management of complex cases. Nevertheless, studies of psychiatric distress among children with cancer have concentrated exclusively on the prevalence of problems within the general patient population (1–3). In a study of 35 children and adolescents undergoing treatment, Kashani and Hakami (3) observed that 17% had *DSM-III* major depression and noted symptoms of anxiety in more than 30% of the patients. Surveys such as these, while helpful, do not specifically address the types of cases encountered when psychiatric consultation is requested. To highlight the particular problems faced by consultants in pediatric cancer settings, we collected information on the reasons for psychiatric consultation in one center and the diagnoses observed.

METHOD

A review was conducted of new psychiatric consultations conducted over 12 months (September 1985 to September 1986) in the Department of Pediatrics at the Memorial Sloan-Kettering Cancer Center. Referrals were made from a 42-bed inpatient unit, a 16-bed day hospital, and additional units with pediatric beds (bone marrow transplantation, intensive care). Fifty-eight patients (38 boys, 20 girls) were seen at the request of their pediatricians. At the time of referral they ranged in age from 2 to 25 years, and their mean ±SD age was 12.6±6.3 years. Eleven patients were 5 years old or younger, 15 were 6–12 years of age, 28 were 13–20 years old, and four were over 20 years old. Every stage of disease was represented, and the time between cancer diagnosis and psychiatric consultation ranged from 2 days to 16 years. Forty-four patients were hospitalized at the time of referral, and 14 were seen in the day hospital. Their medical diagnoses were leukemia (N=22), brain tumor (N=7), lymphoma (N=6), osteogenic sarcoma (N=6), embryonal rhabdomyosarcoma (N=6), neuroblastoma (N=2), Wilm's tumor (N=1), Ewing's sarcoma (N=1), and various hematological conditions (N=7). Forty patients were white, 10 were black, seven were Hispanic, and one was Asian. Thirty-three patients were from two-parent families, and 25 were from single-parent households.

Data were derived from clinical charts and consultation records that included reasons for referral, history of symptoms, mental status examination results, psychiatric diagnosis, and treatment recommendations. In each case the consulting clinician (D.S.R.) had carried out a diagnostic interview with the patient and family, had reviewed the medical chart, and had conducted discussions with the medical and nursing staff. Psychiatric diagnoses were based on *DSM-III* criteria and confirmed by a senior psychiatrist (M.S.L.).

RESULTS

The reasons for referral were evaluation of behavior (N=15), depression (N=14), suicide risk evaluation (N=7), anxiety (N=8), family evaluation (N=5), nausea and vomiting (N=4), change in mental status (N=3), and school problems (N=2). *DSM-III* axis I diagnoses were made in 57 (98%) of the 58 cases. Table 1 provides a breakdown of the primary axis I diagnoses and the age range and mean for each diagnosis.

Four major diagnostic categories—adjustment disorder, organic mental disorder, separation anxiety disorder, and major depression—accounted for 90% of the diagnoses; adjustment disorder was the chief

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TABLE 1. Psychiatric Diagnoses of 58 Pediatric Cancer Patients for Whom Psychiatric Consultation Was Requested

Primary *DSM-III* Axis I Diagnosis	N	%	Age Range (years)	Mean Age (years)
Adjustment disorder	30	52	4–24	12
With depressed mood	18	31	5–24	14
With anxious mood	9	16	4–19	8
With mixed disturbance of emotions and conduct	3	5	5–16	9
Organic mental disorder	8	14	2–25	16
Separation anxiety disorder	7	12	2–16	5
Major depression	7	12	9–24	16
Conduct disorder	2	3	4–16	10
Dysthymic disorder	2	3	20	20
Somatoform disorder	1	2	15	15
None	1	2	13	13

diagnosis (52%). Comparisons were made of the cases in which depressive features were predominant and those in which anxious features were primary. The 27 patients with major depression, dysthymic disorder, or adjustment disorder with depressed mood (mean age=14.8 years) were significantly older than the 16 patients with separation anxiety disorder or adjustment disorder with anxious mood (mean age=7.0 years)($t=4.91$, $df=41$, $p<0.01$, two-tailed).

DISCUSSION

While the pediatric cancer patient is vulnerable to psychological distress, in our study of patients specifically referred for psychiatric consultation, serious psychopathology was uncommon. The most prevalent diagnosis was adjustment disorder, which is similar to findings with adult cancer patients (5, 6). In a parallel review of psychiatric consultations with adult cancer patients, Massie and Holland (5) observed that 64% received the diagnosis of adjustment disorder. At the same time, they concluded that *DSM-III* is not well suited to describing the range of individual responses to medical illness but that adjustment disorder best describes the reactions of these patients in the present classification system. This conclusion also extends to our experience with pediatric cancer patients.

In the present study, careful application of *DSM-III* criteria resulted in the diagnosis of adjustment disorder for patients with a wide range of symptoms. The data also revealed a clear developmental pattern: anxiety reactions were more common in the younger pediatric patients and depressive disorders were more characteristic of the older patients. A similar, but not statistically significant, trend was reported by Kashani and Hakami (3). While these clinical presentations might reflect conceptually discrete syndromes, many investigators contend that anxiety and depression in children are operationally linked and should be viewed as different, age-related expressions of the same phenomenon (7). In all likelihood, the accurate psychiatric diagnosis of children with cancer will depend on general diagnostic advances in child psychopathology.

These findings summarize important features of cases referred to the psychiatry consultation-liaison service in one pediatric cancer center. As pediatric cancer patients face prolonged treatments, transient psychological distress should be anticipated. At present, however, psychiatric consultants must assess complex cases without the benefit of adequate, well-validated diagnostic guidelines. Closer study of psychiatric consultations for pediatric patients is therefore indicated to further understand developmental differences in symptoms and to refine the psychiatric classification of medically ill children.

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Obligatory Associations: A Function of Dreaming

Arthur W. Epstein, M.D.

Some dream images are unequivocally linked to events experienced in the waking state but are not identical. The author refers to such alterations as "obligatory associations"; these serve varied psychical requirements, including cognitive transformation.

(Am J Psychiatry 1988; 145:365–366)

In a self-observation study of the waking event-dream interval (1), I collected 50 dreams. In 32 the dream image was identical to a person or object actually encountered in the waking state; 18 were not identical to the waking event but were unequivocally associated. Why is the dream image not always identical to the waking stimulus?

Table 1 contains the 18 dream images and the associated waking images. In these dream fragments, the dream image did not simply reproduce the waking perception but transformed it. The transformation was slight, and the image was that of an individual, attribute, or idea clearly related to the waking event.

At first glance, it would seem more economical for the dreaming mind simply to reproduce the waking perception. Since this is not always the case, the transformation must have adaptive value. The transformation may involve a matching of associations and a new formation or branching of them. Some of the 18 images matched waking percepts with similar individuals known in the past, some with similar individuals not previously known but seemingly created de novo, some with similar ideas or with objects concretely related in appearance. An automatic process, designed to convert a given waking perception into one closely related, appears operative. This automatic formation of altered but associated images may be called "obligatory association."

Associations in the dream, then, are formed without volition to serve psychical requirements. Among the 18 fragments cited, an element of wish fulfillment may be detected, indicating that the psychical requirements extend beyond elementary cognitive transformation.

TABLE 1. Eighteen Dream Images Associated With But Not Identical to Waking Events

Person, Object, or Event Encountered in Waking State	Dream Image
I drive a car	My sister is driving a car
Blond woman	A different blond woman
Indian neurologist	Indian psychoanalyst
Psychiatry "chair"	Federal Reserve Board
Man with amputation below knee	Woman with bifid leg below knee
White-haired man	A different white-haired man
Attorney reminiscent of Mr. A	Mr. A
Mr. B	Mr. B's wife
I read an article on myelography	I am performing myelography
My two sons are at the table	Two other, younger boys are wrestling
I mention Mr. C's name	I am talking to Mr. C
I return a manuscript to an editor	I have a discussion with the editor
I talk to my wife about psychiatric restraints	I see a female patient in restraints
Man wearing jacket because of cool weather	Heat coming from radiator
I see a woman reminiscent of Ms. D	I am talking to Ms. D
Movie scene of heavy woman carried over threshold	Another heavy woman sitting on my lap
I read Ms. E's name on a program	I see Ms. E, and her visage is slightly altered
Picture of a woman named Ms. F	A man named Mr. F

More complex associative mechanisms were also operative. Such mechanisms relate to the question of why a given waking event is selected for dream inclusion, a fundamental problem of day residue research.

In Freud's view (2), event selection depends on the waking event's availability for connection with an already encoded associative complex, one endowed with affective meaning, which enables the expression or discharge of this "deeper" complex. The dreaming mind selects an event for inclusion and then alters the waking person, object, or event (the associative mechanism of displacement) for modulation ("censorship"). However, in the 18 fragments cited, it would be difficult to claim that the person, object, or event experienced in the waking state was transformed solely for censorship in view of the seemingly simple and affectively neutral quality of many of the persons or objects and their only minimal transformation.

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More likely, two broad types of associative processes are at work in the dream's use of the day residue. In the first, at an elementary level, the waking event is transformed by an automatic matching and branching mechanism. In the second, on a more complex level, the event is transformed by higher processes that subserve, among others, drive reduction and conflict resolution. The first type is not as well recognized in contemporary psychiatric thought and, therefore, is emphasized herein.

To return to the initial question propounded, the dream image is not always identical to the waking perception because there is pressure for association formation. This pressure reflects certain psychophysiological needs as well as the power of "deeper" complexes, as in Freud's view. What are these psychophysiological needs? The matching of new items with the old may reflect the dream's role in memory processing, i.e., bringing new events (short-term memory) into congruence with old encodings (long-term memory) (3). The matching may also consolidate encoded events (strengthening long-term memory). When association formation creates new items (branching connections), this may reflect enhancement of memory and new learning acquisition in REM sleep (4–7), a honing and enlargement of the information base.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHOANALYSIS

The Shame Experience, *by Susan Miller. Hillsdale, N.J., Analytic Press, 1985, 183 pp., $24.95.*

Susan Miller's monograph is based on her doctoral dissertation completed at the University of Michigan in 1981. She interviewed 10 volunteer subjects about their experiences of shame. She terminated each series of interviews when she had learned what she felt she needed to or when the subject began to feel severe distress. This process resulted in a blend of superficial descriptive material and compelling revelations indicating the depth to which the experience of shame affects people. Unfortunately, the author uses this material to make broad and sweeping generalizations about the nature and meaning of shame and, based on those generalizations, about the meaning of emotion. The significance of what might have been an interesting exercise in reportage is further reduced by the fact that it took 4 years to get from dissertation to text. Major shifts have occurred in our understanding of emotion, particularly in our attention to shame, since 1981. Especially unfortunate is the omission of any reference to Wurmser's seminal 1981 text (1), without which any book on shame seems somewhat limp.

What is excellent about this slim volume can be summarized briefly. Miller demonstrates beautifully that each of us has a personal lexicon of emotions and emotion words. She understands that much care is needed to ensure that both members of the therapeutic dyad share definitional systems.

What is wrong with her approach can only be limned lightly in a book review. Miller sees shame and other emotions as ego states deriving from "preconceptual experience." In her attempt to retain the classical psychoanalytic view that important conclusions about development may be drawn from the study of disturbed or unhappy adults, Miller ignores the entire science of infant observation. The theme of such observation is that happy, normal infants are studied in the company of healthy, loving caregivers at home or in settings designed to make them feel at home. Miller states that investigators like Izard (2) described categories of emotion poorly related to adult experience. On the contrary, Izard is one of the many solid, careful investigators of innate affect whose work is drawn in its entirety from the theoretical system introduced by Tomkins (3), which is the basis of all modern work on affect and which is ignored completely in Miller's book.

Books like this only draw one back to Stern's pivotal book (4), which reviews the evidence that affect and affective communication form the major communication system between infant and caregiver and points the way to a system of therapy based on a solid understanding of physiological affect mechanisms, as suggested by Tomkins. Psychiatry simply cannot continue its attempt to explain emotion on the basis of the study of adults. Miller, clearly an intelligent and dedicated psychologist, has been caught in a scientific time warp that has thrust her away from the stream of contemporary research on the nature of emotion.

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DONALD L. NATHANSON, M.D.
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Between Analyst and Patient, *edited by H.C. Meyers. Hillsdale, N.J., Analytic Press, 1986, 268 pp., $29.95.*

This book is the byproduct of a 1981 symposium organized by the Association for Psychoanalytic Medicine, which is linked to Columbia University. A background paper by Lane presents a simple and useful review of the concepts of transference and countertransference both narrowly and broadly defined and from multiple points of view. It is placed, curiously, as the very last chapter. The other papers focus on transference and countertransference in three areas: the analysis of difficult character disorders, analytic brief psychotherapy, and work with and by women.

In the section on difficult character disorders, papers by Aronson, Gedo, Kernberg, and Stein are concisely and critically discussed by Arlow. However, as Stein points out, there is no clear agreement on which patients are difficult, and this is reflected in the diversity of views presented. Arlow cautions against identifying difficulty with primitive conflicts or psychopathology, and Stein notes that all analyses present their own difficulties.

The papers in the next section are also diverse, including Frances's call for systematic research into the indications for transference interpretation in brief treatments, Mann's short discussion of time-limited brief therapy, and Viederman's crisis-oriented psychodynamic life narrative. However, these are tied together by a clear introduction by Perry and Michels and by a discussion by Schafer that is, as usual, elegant.

The papers on analytic work by and with women are written by both women and men: Meyers, Blum and Blum, Person, McDougall, and Liebert. They discuss shifts in therapist gender preference and gender-driven referrals, the impact of therapist gender on the unfolding of the transference, and the homosexual components of female sexuality. There is no summarizing discussion.

This missing third discussion may be one of the three symposium presentations not included in this volume. On the other hand, a quarter of what is included in this book has already been published elsewhere: two (by Gedo and Kernberg) are book chapters and two (by Viederman and Person) are journal articles. Although the book contains some excellent papers that are both thoughtful and thought provoking, this is not a good book. The proclaimed focuses are inadequately defined, and the whole is less than the sum of its parts. Those who plan symposiums need to remember that the criteria defining excellence of a symposium are not identical with those defining a good book. Finally, in an otherwise well-produced book, the number of spelling errors of simple words suggests that the typographer was dyslexic.

WILLIAM A. FROSCH, M.D.
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The Teaching and Learning of Psychoanalysis: Selected Papers of Joan Fleming, M.D., *edited by Stanley S. Weiss. New York, Guilford Press, 1986, 216 pp., $25.00.*

Joan Fleming was an educator par excellence, a pedagogue in the best sense of the word, a woman who began teaching as soon as she was graduated from college and never stopped. She taught biology, physical education, anatomy and physiology, psychiatry, and, finally, completing her analytic training in 1945—when she was a shade over 40—she turned her bent for teaching to psychoanalysis. Her great passionate interest became psychoanalytic education, and she was at pains to point out the peculiar nature of teaching and learning psychoanalysis, relying as it does on the experiential as well as the cognitive mode of understanding. Dr. Fleming's commitment to psychoanalytic education found ample institutional expression. She was for many years dean of education at the Chicago Institute for Psychoanalysis, and she played an important role in the American Psychoanalytic Association, first as secretary of the Board of Professional Standards and then as chairman from 1961 to 1964 (she was one of only two women ever to have held that position).

The broad outlines of psychoanalytic education—the tripartite system incorporating personal analysis, didactic instruction, and control or supervisory analyses—was devised by Max Eitingon at the Berlin Institute in 1925, and it has provided the overall training structure for most psychoanalytic institutes ever since. Dr. Fleming's contribution to the educational process was to refine aspects of this classical approach to psychoanalytic education.

Dr. Fleming's insights and clarifications are detailed in the papers collected in this volume. She recognized that the selection of candidates was a form of prediction of who would or would not do well as an analyst. Through attempting to identify the qualities of a good analyst, she began to define an objective basis for selecting or rejecting applicants for psychoanalytic training. She analyzed the peculiarities of the training analysis and argued that some of its special attributes might be turned to good use. She attempted to spell out the criteria for matriculation and progress of an analytic candidate throughout training and to provide rationales for specific institutional procedures. Additionally, she thought about how to teach the teachers and consequently focused on issues of faculty development. Much of what she advocated has become intrinsic to the organization of psychoanalytic institutes.

Yet and all, how few analysts today know who Joan Fleming was. The reason for this is not hard to understand. Her major contributions were disseminated through her impact on those around her and through the energies she poured into organizational psychoanalysis. Although her book, *Psychoanalytic Supervision: A Method for Clinical Teaching,* written with Therese Benedek (1), is considered a classic, it is primarily known to psychoanalytic educators. None of her other papers could be described as classic; she made no startling discoveries; her name hardly even evokes association with a distinctive point of view or voice other than a staunch adherence to the maintenance of the highest standards for psychoanalytic training. So this book of her selected papers—a kind of homage to her—will be important to serious psychoanalytic educators. The issues she addresses remain timely and fresh, and our thanks go to Stanley Weiss who edited the current volume and who coauthored four of the papers with Fleming.

There may be another homage due Fleming—a book about her rather than a collection of her papers. Aside from her many contributions to organizational psychoanalysis—contributions that have become part of the heritage of psychoanalytic education—there is the intriguing story of her personal career. Born in 1904 in Illinois at a time before many women became physicians, she was the very antithesis of our earliest cultural stereotype of the psychoanalyst. Yet she became a major force in American psychoanalysis. She is described by those who knew her as straightforward, honest, tactful, and solid. These characteristics were all essential to a sometimes fragmented and strife-ridden psychoanalytic movement. Even so, one appreciates those personal characteristics which allowed her to become central to the decision-making processes of psychoanalytic organizational life—a position not achieved by many other female analysts.

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ETHEL S. PERSON, M.D.
New York, N.Y.

Psychoanalytic Process: Theory, Clinical Observation, and Empirical Research, *by Joseph Weiss, M.D., Harold Sampson, Ph.D., and the Mount Zion Psychotherapy Research Group. New York, Guilford Press, 1986, 423 pp., $49.95.*

Among the least attractive traits of psychoanalysis are its religiosity (orthodoxy, knowledge only for the initiated, etc.) and its antiresearch bias. In contrast, this book describes the remarkable research attempts of Weiss and Sampson and the Mt. Zion Psychotherapy Research Group into the process of analysis.

Drawing from implicit concepts in Freud's later works, the authors posit a theory of the unconscious radically unlike Freud's early ideas. They contrast an "automatic functioning" hypothesis, in which a primitive, primary-process, inchoate, and barely knowable id struggles for gratification against an equally unconscious, rigid, and timeless set of ego defenses, to a "higher mental functioning" hypothesis. The latter views the unconscious in dramatically different terms. Less of an unknowable black box, the unconscious of the higher mental functioning hypothesis is goal directed and strives toward freedom from the restricting "pathological beliefs" (neuroses) of childhood. It does this through an unconscious "plan" that takes place in psychoanalysis whereby the individual tests out change by safely expressing some of these pathological concepts in the hope they will be disconfirmed. The individual advances when they are disconfirmed and retreats and regresses when they are not.

Although not invariably incompatible, the two theories frequently lead to different outcomes, which the authors predict and then test. For example, according to the automatic functioning hypothesis, the emergence of previously repressed memories or the frustrations of patients' transference wishes would be expected to lead to increased frustration, anxiety, and regression and decreased cooperation with the analytic process. The opposite is predicted (and borne out) by the higher mental functioning hypothesis, consistent with the authors' view that the unconscious desires to free itself from old pathological views and, when it appears safe to test them, lifts repressions and tests the environment in order to disconfirm them.

Much of this is not surprising. The concept of a useful unconscious certainly makes teleological sense. Such an unconscious is economical, probably contains memory storage (locked and unlocked in varying degrees), and should be equated neither with the id nor with neurosis. Virtually all of the id, most of the superego, and much of the ego are not conscious. To see it in the authors' terms, however, means assigning far more order and planning to the unconscious than we usually do. Weiss and Sampson cite the objections of such theorists as Waelder, Klein, Gill, and Holt, who oppose the higher mental functioning hypothesis as casuistic, unsupported by psychoanalytic data, and insufficiently mechanistic. Hartmann, Kris, Loewenstein, and Rapaport, however, in contrast to both the former group and the authors, feel that the automatic and higher functioning hypotheses are compatible.

The authors' research design grew out of Weiss's earlier, less formalized studies. The primary focus in the present work is the analysis of Mrs. C, a 28-year-old obsessive-compulsive woman who is unable to allow herself pleasure. Tape recordings, tape scripts, and detailed process notes were analyzed by blind raters to compare and validate the two hypotheses. The authors attempted to be rigorously objective in their studies. The treating analyst was geographically and philosophically remote from the research group and its ideas (in fact, he was oblivious to them while he carried out the analysis). Raters were unaware of many of the study's hypotheses and blind to the timing of events (e.g., interpretations and their putative sequelae) to minimize bias.

It is, of course, impossible to entirely objectify what is an essentially subjective endeavor. This work is no exception. The authors are convinced that their views are not compatible with Freud's early views and, although they allow for some combining, they favor replacing over reconciling in a manner reminiscent of some of Brenner and Arlow's proponents, who disavow any current utility to topographical theory. Not all of the authors' study hypotheses were validated by the research, and they are too quick to excuse these discrepancies. Curiously, in describing the patient, the authors never explain what she understood as the reason for her being audiotaped except that "it was for research purposes." What did this mean to her—was she special, atypical, extra eager to please? Surely the taping and being a research subject had some impact, yet this is not elaborated on.

The authors profess openmindedness, but they state that their work cannot be replicated by independent investigators because such investigators would not be able to understand the patient's unconscious plan to overcome pathological beliefs. The investigator would have to come to work with the San Francisco group and learn their theories or have one of the authors decipher the patient's plan and goals. This statement, perhaps, reveals the authors' religiosity. The only other substantial flaw in this work is its repetitiousness—the competing hypotheses are repeated in practically every chapter, and each section recapitulates much of the preceding.

The work is loaded with excellent illuminating clinical examples, and its relevance for psychotherapy as well as analysis is clear. Much of the mystery of what really brings about change in psychoanalysis appears clarified here, and this alone would warrant reading this volume. Not just "inexact" interpretations but "no" interpretations may allow the average psychoanalyst to let the patient's unconscious free itself. Although I am inclined to lump rather than split and feel that both theories are essentially subsumable under the same rubric, there is little question that the authors' research approach and methods represent an extraordinarily important step for psychoanalysis and psychotherapy.

HOWARD S. SUDAK, M.D.
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NEUROBIOLOGY

Animal Models for Psychiatry, *by J.D. Keehn. London, Routledge & Kegan Paul (New York, Methuen), 1986, 238 pp., $42.00.*

This volume joins a growing group of works dedicated to clarifying the role of animals in biomedical research. The problem of justifying animal experimentation would seem more difficult in psychiatry than in other areas because disorders of behavior are usually considered uniquely human. Although the use of isolated tissue preparations in modeling other types of pathological processes is regarded as proper—or even inspired—any suggestion of isolating behavioral processes is often subject to rebuke, suspicion, and rejection (of both grants and manuscripts). Yet it is only through animal experimentation that certain critical neurobiological hypotheses can be tested (e.g., abnormal brain development in young monkeys reared in isolation). The key is to use appropriate animal models while avoiding undue anthropomorphic speculation. This book facilitates this rational process in psychiatry.

J.D. Keehn's book surveys the use of animal behavioral models in biological psychiatry. Since behavior, he argues, is the fundamental unit of data in the description and diagnosis of psychiatric disorders, many questions in psychiatry may be addressed by observation of animal behaviors under conditions in which the relevant variables can be isolated and identified. Keehn therefore asserts that "mental illness may be attributed with doubt or confidence to animals and humans alike according to how public signs of private distress are interpreted" (p. 22).

The book is divided into three main sections. Part one explores the scope, applications, and ethics of experimental biological psychiatry. Part two, entitled Animal Clinical Pictures, relates specific disorders of behavior in animals to their human counterparts. Part three reviews the contribution of animal studies to the human disorders of neurosis, psychosis, drug self-administration, and abnormal development. In each section there is an interesting mixture of studies from ethology and from the experimental analysis of behavior. However, because of the broad scope of this effort, none of these subjects is covered in any great detail. For example, many contributions made in the fields of neurobiology and psychopharmacology are discussed briefly or not at all. The choice of topics may be a result of Keehn's emphasis on homologous models of psychiatric disorders. Homologous models show a correspondence to both the etiology and the result of a human condition. The studies on developmental anomalies, including those of maternal and peer deprivation, best illustrate this approach to animal models. Those models which show isomorphism (similarities to the human disorder in the result of a manipulation only) are represented in studies of movement disorders such as audiogenic seizures and in drug-induced stereotypies.

The chapters on "Behavioural Anomalies and Misdemeanours" and "Animals and Addictions" emphasize the role of conditioning factors in a variety of "pathological" behaviors. Operant studies, through their ability to exactly specify relationships between behavior and controlling environmental conditions, have often been useful in elucidating the genesis and maintenance of such "anomalous" behaviors as schedule-induced polydipsia and drug self-administration. Results of such studies have repeatedly inspired new approaches to the treatment of psychiatric disorders—behavior modification, biofeedback, narcotic antagonist regimens for opiate addiction, and systematic desensitization are just a few. The fertile ground of animal research, Keehn notes, amply justifies the use of animals in psychiatric research and underscores the importance of attention to the public elements of behavior.

The plea for objective measures of behavior is not of recent advent. In his 1950 essay "Are Theories of Learning Necessary?" (1), B.F. Skinner lamented the use of what he termed "theory" in psychology, defined as "any explanation of an observed fact which appeals to events taking place somewhere else, at some other level of observation, described in different terms and measured, if at all, in different dimensions." Skinner's point was not that theory has no place in the study of behavior but that theories should be tested using the same terms and employing the same tools as those in which they were first posed. This argument is nowhere else so cogent as in the use of animal behavior to model behavioral processes in general and psychiatric disorders in particular. The careful selection of animal models in this book facilitates an understanding of appropriate animal use in the study of behavior.

Keehn's terse descriptions of many carefully conducted behavioral studies, often covering disparate areas of psychology, constitute the real strength of this book. Although not well suited as a reference work, it stands in good stead for use by psychiatrists, students, interested laymen, and other individuals who want an introduction to the field of biological psychiatry.

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ROBERT S. MANSBACH, PH.D.
DAVID L. BRAFF, M.D.
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Neuropeptides in Neurologic and Psychiatric Disease: Association for Research in Nervous and Mental Disease Research Publications Series, vol. 64, *edited by Joseph B. Martin and Jack D. Barchas. New York, Raven Press, 1986, 360 pp., $69.50.*

Although psychiatrists remain attracted to the monoamine transmitters as putative dysfunctional agents in psychiatric disorders, the continuing discovery of new neuropeptides has produced a wave of interest in the possible roles of these neuroactive agents in mental illness. Neuropeptides have been implicated as etiologic factors in different neuropsychiatric diseases on the basis of alterations in brain neuropeptide content or changes in plasma neuropeptide levels.

This area of research is very exciting, but fundamental questions regarding the nature of neuropeptides and their functional roles remain unanswered. Of these issues, a major uncertainty involves the exact role peptides play in neuronal transmission. The concentrations of peptides in neurons are substantially lower than those of amino acid or monoamine transmitters. In addition, unlike these more conventional neurotransmitters, neuropeptides cannot be synthesized within synaptic terminals but only on ribosomes within the neuronal cell body. Therefore, neurons that secrete peptides must synthesize them at some distance from the release site and then transport the peptide in a larger prohormone molecule to await final processing near the presumptive release site. Thus, changes in peptide levels may be due to decreased rates of synthesis, increased rates of release, increased rates of degradation of the precursor or final secreted form of the peptide, or outright destruction of the neurons that synthesize the peptide. In addition to these complexities, correlations of changes in peptide content with disease states are confounded by the fact that neuropeptides are not the sole chemical signals secreted by neurons; rather, they seem to act in concert with other neurotransmitters with which they coexist in different combinations in different neurons.

The illustrious contributors to this book have addressed these and a number of other important questions relevant to the understanding of the roles of neuropeptides in normal brain functioning and in human disease states. The opening and closing chapters of the book, by the late Dorothy Krieger and by Floyd Bloom, respectively, are outstanding. Krieger provides a wide-ranging overview of neuropeptides, introducing the reader to a number of issues that are discussed in detail in subsequent chapters. Bloom uses several examples to illustrate the direction of future research involving neuropeptides. The intervening 15 chapters can be divided into two parts. Eight chapters cover basic research issues such as the molecular biology, electrophysiology, and anatomical localization of neuropeptides. The chapters on neuropeptides in the basal ganglia and primate cerebral cortex by Graybiel, Jones, and Hendry are particularly well done and place peptide-containing neurons in the context of the neuronal circuitry of these brain regions. The remaining chapters include a comprehensive review of both basic and clinical aspects of somatostatin, a discussion of the possible role of endorphins in psychopathology, a brief overview of brain grafts in an animal model of Parkinson's disease, and three chapters devoted to Alzheimer's disease. These three represent one of the few shortcomings of this volume in that there is a great deal of redundancy. In addition, some of the material on Alzheimer's disease represents merely the compilation of different measurements of neurotransmitters in this disorder without attempts to consider their relationships or pathophysiological significance. Otherwise, the book is well edited and has an evenness of writing unexpected in a multiauthored text.

Overall this volume provides an excellent perspective on a burgeoning field of research important to psychiatry and is well worth the investment of the interested reader.

DAVID A. LEWIS, M.D.
La Jolla, Calif.

Foundations of Comparative Ethology, *edited by Gordon M. Burghardt. New York, Van Nostrand Reinhold Co., 1986, 432 pp., $48.50.*

This edited book is part of a series called Benchmark Papers in Behavior, which was started in response to the steadily increasing volume of work in different aspects of animal behavior. Each volume is to be a collection of what an expert considers the most significant research in a given area, pulled together in one volume to save students and researchers time and difficulty in retrieving the classical articles themselves and, presumably, to enhance the chances that the original articles will actually be read.

This particular volume comprises articles by scientists whose writings before 1940, mostly pre-1936, influenced Konrad Lorenz in his key theoretical papers. The original articles reproduced in this volume represent a real gem for the historian of this field. There are many early writings about instinct as well as early physiological contributions.

The documents reprinted in this volume contain many of the ideas that eventually came together in the "classical synthesis" of European ethology, a synthesis which came to be most closely associated with Konrad Lorenz and Niko Tinbergen. Their synthesis was built on the ideas contained in the papers reprinted in this volume. Thus, the book provides in one convenient place the writings of those who had considerable influence on Konrad Lorenz and the background material that helped shape what are now known as classical ethological positions. A synopsis of these positions is provided in the introduction to the book and would make worthwhile reading for clinical psychiatrists.

One cannot do justice to such a broad area in a review such as this, but several key points regarding "classical" ethological positions can be summarized. First, the focus of animal behavior research should be on understanding normal behavior in a variety of settings. Experimentation is then based on knowledge of a species' normal behavior (ethograms). Only with these data available can one proceed to an understanding of abnormal behavior that results from manipulation of an animal's ontogenetic development. The importance of evolutionary history and ecological contingencies analogous to a species' anatomy and physiology is recognized as critical in shaping behavior. Also central to classical ethology has been the concept that both heredity and environment affect the phenotypic expression of behavior and that their separate and interactive contributions could be empirically tested. (This concept still gives the field of psychiatry great trouble.) Many papers are devoted to the analysis of instinct and the controversies that pervade this literature. Much ethological literature also deals with fixed action patterns and the role of innate releasing mechanisms and with such important concepts as imprinting, sequences of instinctive behavior, and social displays.

This volume is well organized into five major parts; each contains several reprinted papers about the topic along with the editor's unifying comments, which are quite well done and help orient the reader to each section. The five parts are Darwin and the Analysis of Instinct, Post-Darwinian British Instinct Theory, The Tangled Roots of Comparative Ethology and Comparative Psychology in America, Core Ethology: Precursors of the Classical Synthesis, and The Synthesis Attained. This last section contains a previously untranslated paper by Konrad Lorenz, "On the Concept of Instinctive Action." There are well-done author and subject indexes along with a brief sketch about the editor.

The title and topic of this volume may sound too specialized for most psychiatrists in that they deal with papers published during a period of time that preceded much of current ethological writings. I would share this judgment; however, I liked the original classical papers and enjoyed reading them as they were written rather than other writers' impressions of them. This book is interesting in this regard, and certainly the concepts of "classical European ethology," which these papers helped form the basis of, are critical for psychiatry. Comparative ethology forms one of the basic sciences of psychiatry and will become of increasing importance in future years. It is worth noting that the most recent awarding of the Nobel Prize in medicine in the behavioral area went to ethologists. An evolutionary perspective is critical to the better understanding of our own ontogenetic development, which, after all, is what clinicians deal with on an everyday basis.

WILLIAM T. MCKINNEY, M.D.
Madison, Wis.

Some Simple Concepts and Models, *by Walter W. Surwillo, Ph.D. Springfield, Ill., Charles C Thomas, 1986, 199 pp., $28.75.*

This book is a retrospective look at Dr. Surwillo's work in psychophysiology over the past 25 years. He has been primarily interested in the relationship between EEG rhythms and reaction time in both adults and children. His central thesis is that the EEG alpha rhythm is a manifestation of the activity of pacemaker neurons, which also act to influence sensory processing. He hypothesizes that they periodically gate the sensitivity of other neurons to sensory inputs. The experimental evidence is contained in a series of his published papers. In this book he constructs a neuronal model of the phenomenon to explain the data.

The explanations are clear and the book is well written. I particularly liked his beginning with a simple model and then adding complicating features step by step as he introduces each set of new data. The book also strives to offer complete explanations of other studies that do or do not support Dr. Surwillo's model. The only work to which he refers that is not well explained in the text is the neurobiological work of Lorente de No and Eccles, which provides some of the anatomical and physiological correlates of his models. Better descriptions of their findings would have added a richer neurobiological dimension to the book. For the armchair neuroscience enthusiast interested in models of how neurons might work together to produce simple behaviors, this book is a pleasant night's reading.

ROBERT FREEDMAN, M.D.
Denver, Colo.

PSYCHOTHERAPY

The Evolution of Psychotherapy, *edited by Jeffrey K. Zeig. New York, Brunner/Mazel, 1987, 438 pp., $50.00.*

This volume consists essentially of the proceedings of a conference on the evolution of psychotherapy held in 1985 in Phoenix, Ariz. A potpourri of approaches are represented, and many of the papers are offered by individuals who either originated or developed these approaches. There are presentations and discussions by family therapists, "cognitive/

behavioral" therapists, "humanistic/existential" therapists, psychoanalytic therapists, and different group therapists representing Gestalt therapy, psychodrama, and transactional analysis as well as a section on the Ericksonian approach, all concluding with a final "counterpoint" by that indefatigable iconoclast Thomas Szasz.

The book is attractively arranged and printed; it contains something interesting for therapists of every persuasion. The editor and the other directors of the Milton H. Erickson Foundation evidently went to considerable trouble and expense to organize and publish these proceedings.

The entire book contains a blatant antitraditional psychoanalytic bias and is arranged in such a way as to advertise and promote "Ericksonian" therapy and the Milton H. Erickson Foundation. The careless reader would get the impression that therapy has evolved to a higher and higher level culminating in the Ericksonian approach. In fairness to the book, the bias is clearly stated at the beginning, for example in the statements, "We are moving psychotherapy off the couch. Therapy is more directed to the patient's immediate life situation—for example, by the use of therapeutic tasks and the involvement of the family" (p. xxii) and, "Psychotherapy is moving away from explanations and toward creating constructive experiences" (p. xxiii).

Some of the authors in this collection seem to have been chosen because of their controversial and iconoclastic views, others because of their charisma and audience-drawing power. Certainly some notorious proponents of popular viewpoints are included. From my perspective, which is predominantly psychoanalytic, the section on psychoanalytic therapists is quite weak and does not include any prominent proponent of either traditional psychoanalysis or self psychology. Because of this an alternative viewpoint certainly suggests itself: that the so-called evolution of psychotherapy presupposed by the sponsors of the conference and the book constitutes another effort to evade the hard-won and painful discoveries of psychoanalysis. The reader will have to decide, but the book certainly makes manifest the enormous controversy and disagreement in the field of psychotherapy and the prominent role of charismatic individuals as proponents of different "schools" of thought.

Those psychiatrists who are most interested in a comparative study of the innumerable psychotherapeutic approaches—especially Ericksonian—will find this book valuable, and those who wish to devalue psychotherapy altogether as chaotic and unscientific will find it useful. For an antidote to the views expressed in this book I urge the psychiatrist to read what surely will become a classic paper by Arlow (1).

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RICHARD D. CHESSICK, M.D., PH.D.
Evanston, Ill.

Between Give and Take: A Clinical Guide to Contextual Therapy, *by Ivan Boszormenyi-Nagy, M.D., and Barbara R. Krasner, Ph.D. New York, Brunner/Mazel, 1986, 431 pp., $35.00.*

What is the connection between psychotherapy and morality? The two have been separated by a large conceptual gulf. The classical psychoanalytic position examined what was (in the realm of reality or of the instincts); moral philosophy examined what should be. The analytic tradition located moral judgment in the superego, an agency that the ego and its ally, the analyst, were to view with suspicion. Many forms of family therapy adopted a similar distance from moral questions. This distance often involved taking a position of "neutrality" among the different parties in the family system, finding positive connotations for everything (sometimes even violence and exploitation), emphasizing parental power rather than parental responsibility, and contemplating the automatic operation of the "family system." Indeed, psychotherapies of all kinds have claimed to be "scientific" by looking beyond conventional moral values to define some other system of forces motivating behavior: instinctual drives, self-actualization, behavioral conditioning, social structure, or family structure. Ivan Boszormenyi-Nagy's special distinction has been his ability to construct a therapeutic method from just those moral and ethical materials which the rest of the schools have avoided or tried to reframe.

Boszormenyi-Nagy was one of the founders of family therapy in the 1960s. With the publication of this volume, he again steps forward, with his most recent collaborator Barbara R. Krasner, to define "contextual therapy," the special method and philosophy of working with families that he and his group in Philadelphia have been developing over the past 20 years. There have been two previous presentations with other collaborators, who have helped to make Boszormenyi-Nagy's difficult philosophical style of expression accessible. The first was *Invisible Loyalties* with Geraldine Spark in 1973 (1), which, although it was difficult reading, impressed the family movement with its compelling and original ideas. Clinicians recognized the relevance of these ideas to their intergenerational work with families. Some of the key phrases in this system speak for themselves: "fairness and reciprocity," "systems of merit accounting," and "the parentified child." That book also contained case examples, including detailed descriptions of treatments lasting more than 2 years, which sounded to many of us like the difficult cases we ourselves had to work with. The second presentation of Boszormenyi-Nagy's contextual therapy was a chapter written with David Ulrich in Gurman and Kniskern's *Handbook of Family Therapy* (2). Ulrich contributed a lively prose and a remarkable concentration of the ideas. This chapter is a good introduction for the less devoted reader.

In the book reviewed here, the partnership of Boszormenyi-Nagy and Krasner has produced a fully developed, philosophically expansive presentation of contextual therapy. Krasner is a psychologist who has professorships in the Department of Mental Health Sciences at Hahnemann University and in the Department of Religion at La Salle University. Her voice sounds clearly in this volume, and many of the case examples and the very welcome extended verbatim transcript are hers.

Contextual family therapy has four different levels of focus: 1) facts of life, such as birth order, the death of a parent, and physical illness, 2) individual psychodynamics, 3) the dynamics of family interaction, and, most important, 4) the ethical level of what different individuals think is owed to them, was earned by them, and was given to or taken from them rightly or wrongly. It is thus a system that can include many other views of therapy, notably the object relations psychoanalytic view, and adds the dimension of a way of talking about family relationships as acknowledged or unacknowledged obligations, which is very close to the way many family members think and talk.

Whatever one may think of the theory, this way of using the familiar imagery of ethical discourse is an advantage. Ideas such as "earning merit by being trustworthy" tap into highly valued abstract criteria for behavior and at the same time refer to actions that can be specifically described. There are homely but powerful phrases here, such as "over-giving," which produces guilt, and "delegating parental responsibility" to a child (an idea borrowed from Helm Stierlin), which produces both present and later burdens for the child.

The ideas are most useful in dealing with relations between parents and children, since those relations have the most inevitable moral consequences. The case histories provided are full of the problems of rejection by parents, early death, the loyalty conflicts of divorce, adoption, remarriage, physical illness, migration, and the over- or underresponsibility people feel toward parents and children in those situations.

When it comes to marriage, the authors are only briefly interested in the ethical dimension that Lederer and Jackson (3) described as "the marital quid pro quo," the usually unspoken contract between spouses that, if broken often enough or long enough, will lead the offended party to call the relationship into question. Boszormenyi-Nagy and Krasner begin their exploration on that level, but they then move to the intergenerational aspects of marital trouble. They raise ethical questions, such as, What are the consequences for the children, and what are the roots of marital trouble in the invisible loyalties and unfinished agendas of giving and taking that each spouse brings to the marriage from his or her original family? Parents or siblings may be brought in to settle those scores from the past. The couple is urged to continue trying to "deepen the dialogue" until they find a model for responsibility toward each other that derives from their freedom to give to the other members of their families.

What is this approach good for, and what are its limitations? It is a very positive and powerful metaphor for relationships, offering images that are not based on sex or aggression or arcane "system" mechanisms. Loyalty and responsibility are things everyone has at some time felt good about, but they are not simply positive values. Contextual therapists raise questions such as, How do you decide that you have done enough? How can you free yourself from obligations? They answer, By dialogue with those to whom, realistically or not, the obligations are felt. This dialogue occurs under the sponsorship of the empathically "crediting" therapist.

In addition to its clinical usefulness, contextual therapy makes a really valuable addition to the conceptual vocabulary of relational or interpersonal psychology. For example, one of its central ideas, the idea of "trust," is a quality of relationships between intimates in the family. The ways in which trust is earned, broken, restored, and preserved by deception or in spite of betrayal all have their own relational dynamics that are not simply reducible to other elements of individual psychology. Boszormenyi-Nagy and Krasner describe these dynamics of the earning of trust in a wide variety of family situations.

Whether trust, loyalty, and responsibility should always be the leading metaphors in framing family problems, however, is an empirical question, not a philosophical one. As I read this book I had several criticisms, mostly questioning whether the scheme is as universally applicable as it is presented.

First, Boszormenyi-Nagy says much the same things about treating schizophrenia and other serious mental illnesses in the family context as he said in 1965 (4). Boszormenyi-Nagy implies that these illnesses come out of the relational dynamics of the family and should be treated by addressing those dynamics. Here is a clear case where a medical illness metaphor works better than a child development or family development model, especially one that explores parental responsibility. Indeed, it is hard to tell from the book how the authors would actually treat these illnesses, and I think it would have been a good idea to leave out chapter 2, which refers to them.

Second, the field of family therapy these days is replete with approaches to and books about resistance. This book has a whole chapter on resistance, but I was left with very little sense of what Boszormenyi-Nagy and Krasner actually do to turn the tide in a given situation. Generally, I think, they change the focus to a different relationship than the one under discussion—bring in a new character—and see how that changes the dialogue. They do not approve of techniques like positive reframing or paradoxical prescription as tactics in dealing with resistance, but their own tactical thinking is not satisfactorily described.

Third, I think there are some people in my practice for whom this approach would not work because they do not inhabit the same sobering ethos that contextual therapists do: they do not care enough about their parents or their siblings to make loyalty or indebtedness to them a meaningful category. Some of these are people with whom brief behavioral or strategic approaches work. Depth-dialogue may not be for everyone. This criticism of the book is the same as for other therapies that are based on larger philosophical systems (and have patron philosophers—in this case Martin Buber, in other cases Bateson, Maturana, Freud, or Milton Erickson). The comprehensiveness of the philosophy in these systems has a pickling effect on the self-critical imagination of its proponents. They are not paying attention to the cases where it does not work, and as a result we do not know for whom and how it does work.

In fairness, however, distance from one's own assumptions is rare, even in philosophers and, if one had to choose a single system, the one described by Boszormenyi-Nagy and Krasner would be better than most. On balance, this is an excellent book for family therapists who are ready to add an intrapsychic or new interpersonal dimension to their work, since it offers an avenue to the relational past and the responsible future that has deep meaning to most family members. Unlike many other systems, its language is completely public and sympathetic: the therapist has nothing up his or her sleeve. And that certainly carries the moral relationship between therapist and family in a direction that each side will value.

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The Complex Secret of Brief Psychotherapy, *by James Paul Gustafson, M.D. New York, W.W. Norton & Co., 1986, 447 pp., $34.95.*

Since Freud began the tradition of modern psychotherapy, clinicians have sought effective and parsimonious answers to three interconnected questions: Where is the patient stuck (the problem or pathology)? What experience does the patient need to get unstuck? and How can this experience be facilitated or provided? The history of psychotherapy is the record of attempted answers. Different approaches have all yielded some impressive successes, but each approach has also come up against limitations. In a field full of partial answers, there has been a conspicuous need for an overarching "method of methods" to help guide therapists through potential shoals and impasses to the appropriate methods of intervention with different patients.

The Complex Secret of Brief Psychotherapy is one man's brilliant report of his Homeric journey and "liberal education" as a therapist within the field of talking cures. Dr. Gustafson is Professor of Psychiatry at the University of Wisconsin Medical School and Chief of the Brief Therapy Clinic there. He knows of what he writes and communicates well with a combination of intelligent discourse, clinical anecdote, and literary reference.

Part one, A Method of Methods, contains Gustafson's proposal to take his readers on a long and instructive tour of many different therapeutic approaches, from psychoanalysis through systemic family therapy, in search of a method of methods for knowing which approach to use when "I think my idiosyncratic path may tell the reader something about the virtues and hazards of different methods of brief therapy in the broad analytic tradition" (p. 5).

Part two, An Array of Observing Positions, walks the reader through four different approaches, each increasingly "decentered": psychoanalysis, character analysis, the interpersonal perspective, and the systemic perspective. Each successive approach moves farther from self-interests; each has a widening domain or context. As I understand Gustafson, each observing position has its own purview, its own economy:

> Psychoanalysis sees the hidden demands of the animal in us. The analysis of character sees the "constant attitude" which protects the animal from without. Interpersonal interviewing sees the interactions which tie us into trouble with other people. Systemic interviewing sees these interactions in the service of stable social relations. (p. 6)

One is best equipped if one can reckon from any position, Gustafson argues. The "great guile" of decentering permits more and more powerful interventions while a return to psychoanalysis preserves our individual simplicity.

Each chapter describes an approach, provides a case example from the writings of its originator, gives a modern case example from Gustafson's Brief Therapy Clinic, and discusses the domain and limitations of the approach. We are treated to concise summaries of Freud and Breuer, Ferenczi and Rank, and Reich. We see the first paradigmatic shift from the psychoanalysis of repressed instincts of neurotic patients to Reich's analysis of character, the recognition of the patient's "constant attitude" as the topic of treatment. Gustafson distinguishes the orthodox psychoanalytic "horizontal focus," which follows the thread of contents within a period or sector of the patient's life, from the character-analytic "vertical focus" on the disturbance through the layers of content (pp. 25–26).

The "interpersonal perspective" is represented by the well-described virtuosity of Alexander and French, Sullivan, Winnicott, and Balint. There is such rich material here that no brief summary could do it justice. Gustafson quotes a famous passage from Alexander and French's 1946 book on psychoanalytic therapy (1) comparing the therapist at the beginning of a case to "*a traveler standing on top a hill overlooking the country through which he is about to journey.* At this time it may be possible for him to see *his whole anticipated journey in perspective*" (pp. 36–37; Gustafson's italics). Each interpersonally oriented therapist described here is brilliant, original, and experimental in what he sees and how he journeys. Each is hopeful and able to go to the heart of the matter with great economy and sensitivity, recognizing both the patient's problem and the patient's worthwhile strengths. Winnicott's single-session consultations, Balint's relatedness with a paranoid patient, and Sullivan's search for the commonsensical solution all emphasize the patient's social adaptation. Gustafson sings their praises: "Who else could be so catholic about potential adaptation, so trenchant when necessary, and yet so unorganized when necessary? Only Balint, Winnicott, and Sullivan that I know, which makes them my favorite trio in the realm of psychotherapy" (p. 86).

After a valuable side trip through the ideas of Gedo and Havens to help enhance our sense of the limiting complexity of developmental deficits and the importance of meeting the patient where he or she is, Gustafson reviews in four chapters the best known modern brief therapists. Again, cases are presented and critiqued with a discussion of the domain of each therapist's technique. Gustafson summarizes them well:

> For Malan, the stories are about patients who are devoted to their duty, narrowly, until the therapist helps them to discover their opposite true feelings. For Mann, the stories are of patients who have struggled so long and hard to be something worthwhile, but, in spite of their best efforts, they find themselves back in pain. For Sifneos, the stories are of patients who pretend to be children sneaking around with sexual interests, because they are afraid to own up to their powerful, adult, sexual demands. For Davanloo, the stories are of patients who sit passively behind walls of vagueness, until the wall is destroyed by the therapist, whereupon the patient has a breakthrough into true feeling. . . . It is remarkable how each of these four therapists generates his own class of story over and over again. (p. 133)

Gustafson sees the success (and failure) of each approach and cautions against becoming an overly enamored one-trick dogmatist, a devotee of the school of Davanloo or Sifneos or whatever. He has seen the Procrustean danger: "All you have to do is get a procedure you are comfortable with, get a supply of patients who are comfortable with your procedure, and forget those who don't fit in with your procedure [or blame them for being resistant, unmotivated, or ego deficient]. The patients fit you, and not vice versa" (p. 214).

The systemic perspective is the fourth, most decentered perspective, involving a new epistemology with circular (nonlinear) thinking. Gustafson draws upon Bateson and the Milan family therapy teams (Selvini Palazzoli is the best-known figure) to present the logic and methods of the systemic approach. He describes the opening moves, middle game, and end game of the Milan school. Families (like all systems) ensnare their members in labyrinthine games. They are "autopoetic" (self-regenerating), and the intrepid therapist dealing with someone caught in such a web (and trying not to get entangled) will need to meet, as Gustafson puts it, "the requirement for mapping onto maps of greater logical complexity than the event mapped, and the requirement for positive connotation of the event to capture the ears of the players" (p. 228). Gustafson's clinical examples help make this less confusing as we recognize how an identified patient may be held in place if any attempted change simply reinforces the existing system. Particularly in the end game do we see that the patient's "problem" is often insoluble within the class of experiences and actions allowed to loyal family members—even in individual therapy we need to consider "the other people in the room." Gustafson tries to further illuminate the systemic perspective with a discussion of Maturana's theoretical biology, but most readers will probably find this section abstruse rather than enlightening, a rare lapse from what is otherwise literate lucidity—Gustafson recognizes this himself and good-humoredly advises the reader unwilling to devote 2 years to the passage to skip ahead eight pages (p. 241).

Parts three and four elaborate the method of methods. The key is to find how the patient stays the same:

> The patient can be seen to be organized in a singular way to come round to a recurrent powerful desire, to hold to a constant attitude, to defend something worthwhile from other people, to continue a family game. The appreciation of this singular organization allows the patient latitude about how this necessity may be achieved. No patient needs help to change, only help to discern what has to be held at all costs. (p. 263)

Here the therapist's ability to shift perspectives is essential:

> This is the complex secret, to keep this range of positions for observation. . . . I describe a brief therapy which is brief by virtue of the economy of conception, rather than brief by virtue of limiting the time in advance. . . . I do not propose any attempt by the therapist to change the patient. No such finagling is described or necessary. My entire aim is to be clear about what the patient has to hold onto or conserve. Such appreciation will allow the patient many new moves. (pp. 274, 279)

The author then takes us through the opening moves, middle games, and end games of several brief (and not so brief) therapies, illustrating the value of the multiple perspectives and their attendant techniques. He shows us how to succeed and how to stay the same.

Part five, Learning Problems, discusses some issues of supervision and teaching/learning. Considerable wisdom is summarized in the comment, "We are part of the equation" (p. 340). Still, I would have liked more discussion here about problems that may interfere with the learning and practicing of brief therapy, factors that I have described elsewhere (2) as therapist resistances to brief therapy: the belief that "more is better," the myth of the "pure gold" of analysis, confusion of patients' interests with therapists' interests, the demand for hard work, economic and other pressures, and countertransference and related therapist reactions to termination of therapy. (Gustafson's discussion of the end game in which the patient subtracts the therapist from his or her life is highly instructive and provides some caution about how therapists can interfere with this crucial closure.) An appendix of follow-up interviews of cases described in the text and a section of interesting notes rounds out the book, along with an index and extensive bibliography.

Gustafson works within the psychodynamic tradition. I would have enjoyed his considering other approaches to brief treatment, such as Gestalt therapy, Ericksonian techniques, and transactional analysis, although he makes it clear that he is describing his path of understanding and not claiming a monopoly on the truth (p. 7). His "secret"—to allow change by understanding the ways of sameness—is appealingly Zen-like in its paradox. I would add a second, complementary "secret": change becomes easier when patients deeply experience their autonomy and responsibility. Therapists too often encourage patients' stuckness and passive positions as victims by reinforcing the fiction of "thoughts coming into your mind" and "complexes operating within you" rather than helping patients see that they choose, think, scare themselves, and depress themselves (3). It is noteworthy that several studies with long-term follow-ups (4–6) have reported favorable results after even a single interview oriented toward increasing patients' sense of personal responsibility and insight into their core conflicts.

The Complex Secret of Brief Psychotherapy is an insider's book, best appreciated by those who have labored in many of the same vineyards and who have already developed a nose for some of the different varietals. Beginners can learn much here, although it is not an introductory book but, rather, a brilliant meta-level integration. Another of Gustafson's favorite quotations comes from Sullivan in 1954 (7): "I think the development of psychiatric skill consists in very considerable measure of doing a lot with very little—making a rather precise move which has a high probability of achieving what you're attempting to achieve, with a minimum of time and words" (p. 330). *The Complex Secret of Brief Psychotherapy* is a major contribution, full of powerful concepts and interesting nooks and crannies. Anyone who truly grasps what it offers will be the richer.

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Handbook of Cognitive Therapy Techniques, *by Rian E. McMullin, Ph.D. New York, W.W. Norton & Co., 1986, 342 pp., $34.95.*

Have you ever thought about responding to a depressed patient musing about his intellectual inferiority with this Will

Rogers quote: "Everybody is ignorant, only on different subjects"?

Humorous counters to dysfunctional thought patterns is one of a series of more than 70 techniques presented in this volume. The techniques are presented in chapters grouped into topics entitled "Countering Techniques," "Perceptual Shifting," "Conditioning Techniques," "Paradoxical Methods," "Logical Analysis," "Adjuncts," and "CRT [Cognitive Restructuring Therapy] Tools." Dr. McMullin presents this book of techniques for therapists already familiar with the basics of cognitive therapy, primarily identification of thought, beliefs, and schemata producing negative emotion. The focus of this volume is producing change in the dysfunctional belief system of patients, relying heavily on Dr. McMullin's experience over 16 years of using cognitive therapy as well as the work of Albert Ellis and Aaron Beck.

This book is well written and referenced, also at times entertaining. The techniques used in cognitive restructuring therapy extend beyond standard cognitive methods to include methods based more on experimental, behavioral, and psychodynamic models. Individual techniques are presented in a standard format, beginning with principles and methods followed by an example, often from Dr. McMullin's experience. The sections end with comments and sources of further information.

Although the sections are highly structured, there is little emphasis on diagnosis before beginning a series of techniques and little to help one in deciding which technique is best to start with for a particular patient. McMullin does provide suggestions for monitoring response to individual techniques and suggests use of a series of techniques until improvement is noted. Although this "experimental" approach to methodology does not differ from some standard somatic psychiatric approaches (for example, trying another tricyclic if the first one fails), it does not provide much guidance for the novice therapist. In this sense the volume fails as a treatment manual in the manner of the major works of Aaron Beck et al. on cognitive therapy of depression (1) and anxiety disorders (2). Beck's highly structured approach simplifies the timing and manner of intervention and provides more emphasis on the importance of diagnosis.

The volume does not address the issue of effectiveness of medication combined with psychotherapy. Panic attacks with agoraphobia are mentioned quite frequently as amenable to cognitive restructuring therapy. Patients with panic disorder with severe symptoms deserve trials of medication in conjunction with psychotherapy and may actually profit more from cognitive intervention when anxiety levels are controlled.

Despite the limitations mentioned, this volume deserves serious consideration for psychotherapists doing cognitive therapy. By reading it they will be able to respond to a social phobia patient's concern about being respected with this anonymous quotation: "Do not worry what people are thinking about you for they are not thinking about you. They are wondering what you are thinking about them."

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GERIATRICS

Senile Dementia of the Alzheimer Type: Proceedings of the Fifth Tarbox Symposium, *edited by J. Thomas Hutton and Alexander D. Kenny. New York, Alan R. Liss, 1985, 389 pp., $98.00.*

This book provides a useful update on advances in Alzheimer's disease research. In addition, the volume offers valuable contributions in areas of management and treatment of Alzheimer's disease. The symposium on which it is based was held in Lubbock, Tex., in October 1984.

The book is divided into five parts. The first part consists of newer evaluation methods (saccadic eye movements, positron emission tomography scanning, and neuropsychological techniques), management techniques (nonverbal communication, the burdened caregiver, and family conflicts), and behavioral and pharmacological treatment. The second part deals with the related disorders of Parkinson's disease, lacunar dementia, and the parkinsonism-dementia complex. The third part of the book addresses the epidemiology and genetics of Alzheimer's disease. The fourth part deals with basic science topics, including the cholinergic system, morphology, immunology, different trace elements, and two potential methods of treatment for Alzheimer's disease (the sulfonyl fluorides as long-acting cholinesterase inhibitors and intracerebral transplantation of cholinergic neurons). The fifth and final part of this book provides a national overview and possible future directions in research and health care delivery relevant to Alzheimer's disease.

A unifying theme that emerges repeatedly is the hypothesis that dysfunction of the blood-brain barrier may interact with factors in the pathogenesis of the disease. Wisniewski presents evidence of blood-brain barrier dysfunction in scrapie-infected sheep. Mortimer and Hutton present epidemiologic evidence of a higher rate of head trauma, an insult known to bring about transient disruption of this barrier, in Alzheimer victims. Nandy presents evidence of the importance of brain reactive antibodies, especially when associated with mechanical damage to the blood-brain barrier. Fillit presents evidence that antibrain antibodies in Alzheimer's disease have a special affinity for the functional sites for choline acetyltransferase, which are known to be particularly susceptible to degeneration in Alzheimer's disease. Thus, the book offers an exciting new conceptual framework in which to explore the pathogenesis of Alzheimer's disease and suggests the need for future studies of blood-brain barrier competency in Alzheimer's victims.

Readers interested in Alzheimer's disease research who find this volume rewarding will also enjoy the volume by Crook et al. (1) for additional reading.

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Alzheimer's Dementia: Dilemmas in Clinical Research, *edited by Vijaya L. Melnick and Nancy N. Dubler. Clifton, N.J., Humana Press, 1985, 344 pp., $34.50.*

This book deals with an extremely important but much more specific topic than the title suggests. With the exception of a brief and general introductory chapter by Robert Katzman, the authors focus on issues related to the protection of human subjects in Alzheimer's disease research. Ethical and legal issues related to clinical research are considered and specific topics related to informed consent are discussed from different perspectives in the 20 chapters of the volume. The final chapter presents guidelines for addressing ethical and legal issues in Alzheimer's disease research that were developed following a 1981 National Institute on Aging conference on the topic. Indeed, chapters in the book are expanded and updated versions of papers presented at that conference.

The ethical and legal dilemmas inherent in Alzheimer's disease research are certainly profound, and there are many difficult questions that must be addressed as investigators begin to explore such dramatic new therapeutic possibilities as intrathecal drug delivery and brain tissue transplantation. Persons who conduct, administer, or regulate such research will find this volume a useful resource as they consider the difficult problems and exciting scientific possibilities that lie ahead.

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Senile Dementia of the Alzheimer Type: Early Diagnosis, Neuropathology and Animal Models, *edited by J. Traber and W.H. Gispen. New York, Springer-Verlag, 1985, 365 pp., $49.00.*

Does the world really need another proceedings of a symposium on Alzheimer's disease? It is hard to make a favorable case for such an undertaking, but this volume may be an exception, at least in some parts.

The symposium was the Second International Tropon-Bayer Symposium on Aging of the Brain held in Cologne in November 1984. This volume is the second in the series Advances in Applied Neurological Sciences, edited by R.J. Joynt and A. Weindl.

This book is divided into several sections. The first section is concerned with diagnosis. Useful rating scales and psychometric instruments associated with the names of some of the authors (B. Reisberg, R.C. Mohs, S. Kanowski, and J. Jolles) are included. There are also good reviews of higher mental functioning in Parkinson's disease (by A.J. Lees), of positron emission tomography and nuclear magnetic resonance imaging, and of regional blood flow in the brain.

The remaining sections suffer from the time elapsed since this symposium was held. Enough has happened since 1984 to make many of its questions irrelevant or uninteresting. Not that many of the questions have been answered comprehensively; rather, new information has shifted the spotlight. Two chapters do contain useful collections of data: H. Haug describes his research into the extent of neuron loss throughout life (the results are encouraging) and J.M. Candy et al. review the contribution of aluminum and silicon to Alzheimer pathology.

I must give this book only lukewarm endorsement. There are good chapters and I did not recognize any bad ones. The index seemed unusually useful. But most readers interested in Alzheimer's disease would do better with proceedings from a more recent symposium.

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Recent Advances in Psychogeriatrics, 1, *edited by Tom Arie. Edinburgh, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1985, 228 pp., $37.50.*

This work is the first volume in a series designed to present new information in the rapidly changing field of psychogeriatrics. A particular emphasis is on the dementias. This first volume appears to accomplish its goal.

I believe the emotional starting point for this work is the frustration of many of us in the field at reading the same information over and over again in the unending series of symposium proceedings on aging. Every volume seems to start with the neurochemistry of the aging CNS. The articles in this work appear to be designed to briefly review what is old news and then spend most of their effort on highlighting new and controversial material and developing interesting new ways to look at the field.

An example of this approach is "Survival in Dementia" by Christie. This article addresses the interesting question of how long dementia patients survive and what factors go into length of survival. It enumerates the different factors found in many different studies that relate to this central question. Thus, the author does some interesting summarizing work for the reader rather than just presenting the dry abstracts of a number of related articles.

Another example of this approach is the article by Roth and Wischik on the heterogeneity of Alzheimer's disease and its implications for scientific investigations of the disorder. Again the authors move quickly to interesting and useful information on the subtyping of the dementias. They go into the different ways to classify dementias (clinically, biochemically, and pathologically) and discuss the implications of each approach. In this manner a useful and interesting theme becomes the center of what could have been a boring article recounting the different diagnostic criteria for the dementias.

Unfortunately, not all the articles in the volume can meet these innovative standards; however, they all try. In general the editor should be encouraged in this direction. One would hope that the next volume will deal with rapidly progressing news such as the genetic and biochemical markers proposed for the disease.

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Handbook of Geriatric Psychopharmacology, *by Michael A. Jenike. Littleton, Mass., PSG Publishing Co., 1985, 157 pp., $20.00.*

Books with the word "handbook" in the title seem to fall into two general classes. In recent years, there have emerged a number of large, heavy tomes used mostly for reference. Although these may be valued for one's office library on occasion, they are bookstand or desk top works unmanageable by those of us doomed never to play professional basketball. Michael Jenike has departed from this trend in his handbook. In many ways this slim, helpful volume is reminiscent of those soft-cover "bibles" that were the valued investments of my house officer days in medicine. This handbook contains useful clinical information organized in a logical manner and is complete with simple tables and formulas to help the primary care clinician in making judgments about appropriate medication for older patients. Dr. Jenike has a clear and straightforward writing style that is particularly praiseworthy, and this book should pass muster among our primary care medical colleagues on stylistic grounds as well as for its excellent clinical content.

In choosing to be brief, errors of omission will naturally occur. Perhaps more emphasis should have been placed in different places on alternatives to medication, on the important roles of family (and patient) counseling and psychotherapy, on support groups, on routine exercise, and even on diet as valued alternatives and/or adjuncts to the therapeutic regimen. For a book intended for primary care physicians, omission of the importance of appropriate referrals to other medical and nonmedical professionals and community groups is troublesome. Social work and legal assistance are mentioned in the chapter on Alzheimer's disease, however.

Troublesome, too, in the relatively extensive section on psychostimulants is the failure to discuss relative risk-benefit ratios or the importance of limiting their use over time, aside from reminding the reader that such medication may be illegal or unacceptable under certain conditions.

In developing his valuable decalogue of hints for the prescribing physician, Dr. Jenike might wish to borrow my first rule of therapeutics: anything that can help can harm. This is particularly the case for older patients in whom social and psychological variables often present as clinical psychiatric problems and warrant careful diagnosis.

In reviewing medical causes of depression, anxiety, and other psychiatric disorders and symptoms, the handbook is comprehensive, on target, and valuable for all of us in psychiatry. It is eminently practical in listing foods and medications to be avoided with monoamine inhibitors, giving lists of drugs by classification with side effects as well as typical doses, and offering a wide range of therapeutic alternatives within the biological sphere. The bibliography reads more like old friends than new data but is valuable nonetheless.

The book is by design a small, focused work on an important aspect of clinical practice and a helpful addition to one's office library, ideally in close proximity to the *Physicians' Desk Reference.*

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Depressive Disorders in 100 Adolescents Who Attempted Suicide

SIR: One hundred adolescents (31 male and 69 female), 13–18 years of age, consecutively hospitalized in an adolescent psychiatry service after attempting suicide were evaluated by one of us (H.C.), a pediatric psychiatrist, in a clinical interview directed to the diagnosis of affective disorders according to *DSM-III*. Of the 100 adolescents, 81 were found to have major depression. However, 32 of these subjects met the criteria for dysthymic disorder as well (double depression). Ten other adolescents were found to have dysthymic disorder only. Hence, 91 adolescents met the criteria for *DSM-III* depressive disorders.

Our data support the strong relationship between depression and adolescents' suicide attempts that has already been observed in other studies. Crumley (1) found that 33 of 40 adolescents who attempted suicide had an affective disorder, and Friedman et al. (2) observed that 27 of 28 adolescents who attempted suicide had affective disorder diagnoses according to *DSM-III*. Robbins and Alessi (3) also found that suicidal behavior was strongly associated with depression in adolescents: seven of 15 adolescent inpatients who had made two or more suicide attempts had a major depressive disorder, and five of the six patients who had made medically serious suicide attempts had diagnoses of major depressive disorder, melancholic. The remaining patients had a dysthymic disorder.

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Alprazolam Plus Buspirone in Treatment of Anxiety

SIR: Single-drug pharmacotherapy of several *DSM-III* axis I disorders may achieve partial or no clinical response. One alternative is a combination drug strategy, for example, a tricyclic antidepressant plus lithium. Combination strategies may offer a synergism—pharmacokinetic or pharmacodynamic (e.g., an augmentation of a receptor system)—resulting in an amplified response.

The pharmacotherapeutic mainstay of treatment for anxiety has been the benzodiazepines. Their putative mode of action includes several mechanisms (1). During acute pharmacotherapy, a single benzodiazepine may be effective in approximately 65% of patients (2). Higher doses carry the risk of increased side effects and dependency, without clearly documented gains in therapeutic efficacy.

Recently, a series of nonbenzodiazepine alternatives, including the azaspirodecanedione buspirone, have been investigated (3). While chemically unrelated to the benzodiazepines, buspirone exhibits similar anxiolytic indications and efficacy (3). In contrast to the benzodiazepines, buspirone apparently enhances hippocampal dopaminergic and noradrenergic cell firings while decreasing striatal levels of serotonin activity (type 1 receptors). This compound challenges the concept of a single neuroregulator of anxiety. Accordingly, Eison and Temple (4) have proposed a mechanism that has an interface with several neurochemical axes.

We have recently seen five ambulatory patients (three male and two female; ages 21–45 years) who met the *DSM-III-R* criteria for the axis I diagnosis of generalized anxiety disorder. All of these individuals had had previous exposure to benzodiazepines (duration, 4–12 months), three of them at the time of initial evaluation. Previous responses had been partial, with mild to moderate side effects.

Nonblind assessments of these patients were made by means of the Hamilton Rating Scale for Anxiety and the Hopkins Symptom Checklist-56 (SCL-56) at the beginning of the study and bimonthly during three consecutive treatment phases: 1) benzodiazepine (alprazolam), 2) tapering of the alprazolam with concurrent buspirone, and 3) combined buspirone-alprazolam. Each drug assignment was for 6 weeks to the maximum tolerated/effective dose. In anxiolytic efficacy buspirone plus alprazolam ranked first, alprazolam alone ranked second, and buspirone alone was third. Patients' scores on the rating scales revealed overall improvement (entrance score minus conclusion score for each treatment phase) as follows: for alprazolam only, Hamilton scale score=7.3, SCL-56 score=15.1; for buspirone, Hamilton scale score=6.7, SCL-56 score=11.9; for buspirone plus alprazolam, Hamilton scale score=12.7, SCL-56 score= 24.3. The small sample size prohibits statistical analysis. In this group, no further improvement was realized upon a change to buspirone alone (phase 2). However, when both agents were used concurrently, a greater degree of symptom relief was observed. No selective changes in individual scale or item scores emerged. We cannot exclude a time effect, as buspirone plus alprazolam was the final treatment in each case.

This observation suggests a possible strategy for partial responders with generalized anxiety. An enhanced serotonergic profile manifested by a benzodiazepine (4) with buspirone (5) or alternative unique neurochemical properties could explain a synergistic advantage in certain refractory patients. If clinical anxiety is the product of a complex interaction of multiple neural systems, the combination of a benzodiazepine and buspirone may best diminish the arousal, attentional, and behavioral aspects of anxiety. As was observed here, it may allow the use of lower doses of both drugs than if either was used alone, minimizing side effects, physical tolerance, etc.

Obviously, much work needs to be done to determine whether there is an "optimal patient" for combination therapy and to document efficacy. Such tandem drug assignments are inappropriate without careful antecedent trials of each agent alone. We encourage more formal investigations into the possible relationships between drugs which are administered together.

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Verapamil Caused Depression, Confusion, and Impotence

SIR: I recently had occasion to hospitalize Mr. A, a 45-year-old white male accountant, for suicidal depression and impotence. His physician had placed him on a regimen of verapamil for hypertension about 4 months before his admission. Soon thereafter, according to his wife, he had become depressed, impotent (including the loss of his normal morning erections), and confused. He had never had a history of angina, congestive heart failure, or arrhythmia.

Mr. A had called his physician on several occasions before his hospitalization, indicating that his blood pressure was not normalizing with the verapamil treatment and describing his erectile difficulties. The physician asked him to increase his dose of verapamil, but his blood pressure remained abnormally high.

At the time of his admission to our psychiatric hospital, Mr. A was taking 240 mg of verapamil every morning and 120 mg at bedtime. His thinking was circumstantial and convoluted, but he was not delusional. He was markedly depressed and fearful that his wife of 18 years was going to leave him (even though she had indicated to him on many occasions that she intended to work this through with him). He was suicidal but had not tried to harm himself. He had a mild toxic organic brain syndrome. His diastolic blood pressure on admission was 120 mm Hg.

After talking with his physician, we decided to obtain cardiologic consultation. The physician and the cardiologist recommended discontinuation of verapamil. Treatment with hydrochlorothiazide/triamterene, one capsule twice a day, was instituted. Mr. A's blood pressure normalized instantly, with diastolic readings hovering around 90 mm Hg. Within 36 hours he had had four erections, and within 72 hours his convoluted thought process had improved and had become goal oriented. His depression lifted within 36 hours as well.

I am aware that the *Physicians' Desk Reference* lists confusion, fatigue, and impotence as occurring in 0.5%–1.1% of patients who are taking verapamil. During Mr. A's hospitalization, in several conversations I had with the physician, another family physician, and the cardiologist, I realized how innocuous verapamil is made to seem by representatives of pharmaceutical companies. My observation is that verapamil is an exceedingly complex compound, and psychiatrists and general physicians should be alert to possible adverse reactions.

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Problems in Managing a Schizophrenic Patient With AIDS

SIR: There is an abundance of literature concerning psychiatric complications of acquired immune deficiency syndrome (AIDS), the attitudes of ward staffs toward psychiatric patients with AIDS, and handling medical emergencies of psychiatric inpatients with AIDS, but very little information exists in today's literature concerning the management of schizophrenic patients with AIDS. The long-term management of a schizophrenic patient with acquired immune deficiency presents a dilemma in terms of giving optimal treatment to the patient without posing unnecessary risks to others.

An increasingly large number of schizophrenic patients who test positive for the human immunodeficiency virus (HIV) are presenting to psychiatric wards. Quite often they lack the insight necessary for them to be educated on even the basic principles of disease control. Once these patients pass the acute crisis that was initially responsible for the admission, there are two long-term treatment options: discharge them back into society, knowing that many people will be at risk of exposure, or institutionalize them indefinitely, at the risk of exposing the inpatient population while hospitalizing a patient who may otherwise not need long-term inpatient care. From a legal standpoint, we might not even have a second option, since it might be difficult to prove that others would be in imminent danger if these patients were released.

This issue has been addressed in Great Britain, on the basis of the Public Health Act of 1984, in the case of a patient with AIDS who was requesting discharge from the hospital although he was actively bleeding (1). Thompson et al. (2) mentioned the problem of treating a psychiatric patient with AIDS in a case in which the patient was deliberately cutting himself while in the hospital. His final disposition was imprisonment for an unrelated incident.

We present the following case in point.

Mr. A, a 28-year-old man with a 7-year history of paranoid schizophrenia, was admitted to our hospital because he was wandering the streets in a dazed state and refusing to take medication and baths. During an admission 9 months earlier, he had been found to be HIV positive after giving a history of homosexual activity and intravenous drug abuse. During the current hospitalization he was found to have AIDS-related complex. Numerous attempts were made to educate him about proper personal hygiene and infection control, but he consistently demonstrated only minimal understanding of his situation. He frequently would urinate on the walls and in other public places and share drinks, food, and cigarettes with other patients. After several weeks of supervised chlorpromazine administration, his behavior improved markedly, but he continued to show little understanding of his disease. Ultimately, Mr. A was discharged to the care of a relative who exhibited an adequate understanding of AIDS and the required precautions.

The question of optimal patient care versus maximal protection of society that arises with respect to the disposition of patients such as ours remains unanswered.

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Lithium Therapy in Carbamazepine-Induced Agranulocytosis

SIR: We report a case of agranulocytosis in a patient previously treated with carbamazepine and lithium that was resolved with lithium therapy.

Mr. A, a 38-year-old man with a history of hospitalization for mania and depression, was admitted to the hospital with acute mania. Different psychotropic medications, including haloperidol, chlorpromazine, cyamemazine, and benzodiazepines in various combinations, had been tried with no success. These medications were stopped, and the patient was given combined carbamazepine (600 mg/day) and lithium (750 mg/day) therapy. Twenty-one days later, the patient developed an itchy maculopapular rash on his trunk, limbs, and scalp. A blood count revealed a WBC of 2.5×10^9/liter, with 0.05×10^9/liter neutrophils. The agranulocytosis and skin reaction were attributed to the exposure to carbamazepine medication. The drug was stopped, and lithium carbonate was continued, at a dose of 1,000 mg/day. The hemoglobin concentration and platelet count remained normal. A bone marrow biopsy showed marked hypoplasia of the myeloid series. The next day, the total leukocyte count was 0.6×10^9/liter, with no detectable neutrophils. After 3 more days, the neutrophil count had returned to 2×10^9/liter, and Mr. A's cutaneous eruption had resolved. There was no fever and no further episode of infection.

Carbamazepine and lithium have been reported to have synergistic effects in the treatment of affective disorders (1). Reactions to carbamazepine, including rashes and depression of bone marrow ranging from leucopenia to aplastic anemia, are thought to be idiosyncratic and may be due to hypersensitivity and formation of immune complexes (2). Agranulocytosis is a rare hematological side effect of carbamazepine; four reports of it have been published (3), as far as we know.

Although the mechanism is not established, studies have suggested that lithium increases granulocyte production (4). Stein et al. (5) evaluated the ability of lithium to affect the neutropenia associated with cancer therapy. The administration of lithium to patients with Felty's syndrome raises the neutrophil count. Our report shows that lithium carbonate can cause this kind of substantial increase in a patient with carbamazepine-induced agranulocytosis. To our knowledge, this is the first report on the effect of lithium carbonate in agranulocytosis secondary to carbamazepine administration. Lithium therapy may be helpful in patients with drug-induced agranulocytosis.

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Bromocriptine Treatment of Cocaine Abuse in Patients Maintained on Methadone

SIR: Cocaine abuse has become a major problem in methadone maintenance programs (1). Bromocriptine has been used to treat cocaine abusers who are not in methadone programs, but researchers have obtained conflicting results (2, 3). Dackis et al. (2) reported decreased cocaine craving with minimal side effects, while Tennant and Sagherian (3) found no significant efficacy and substantial side effects from bromocriptine. No studies that we are aware of have reported using bromocriptine for cocaine abuse among patients maintained on methadone.

In a pilot study, we gave bromocriptine, 2.5 mg/day, to six cocaine-abusing methadone patients for 4–8 weeks (mean=5 weeks). The patients had a mean age of 33 years (range, 27–40 years), were white, and included two men. All six were daily cocaine users at entry into this study, and five were intravenous cocaine users. Patients were maintained on a stable dose of methadone during the trial (mean dose=60 mg/day, range=50–75 mg/day) and came into the clinic 7 days a week for observed ingestion of their methadone and bromocriptine. Cocaine use was monitored by weekly urine tests and self-reports. Cocaine craving (rated on a 20-point scale) and side effects were monitored daily during week 1 and then weekly, as described elsewhere (4).

Of the six patients, four reported more than 50% decreases in cocaine craving within 2 days of starting the bromocriptine, and these same patients had substantial reductions in cocaine use verified by urine tests. Weekly cocaine use for all six patients dropped significantly from a mean±SD of 4±3 g/week to 1.9±4 g/week ($t=2.6$, $df=5$, $p<0.05$). Mean cocaine-craving scores dropped from 13.3 to 5.8 ($t=2.7$, $df=5$, $p<0.05$). The two nonresponders (one had severe nausea when taking bromocriptine) were subsequently hospitalized for cocaine abuse treatment. Three patients reported side effects from the bromocriptine: two had severe nausea (one was the nonresponder) and one had daily headaches. These side effects decreased after the dose was reduced to 1.25 mg/day at the end of the first week, while efficacy was maintained for the two responders.

The significance of intravenous cocaine abuse by patients in methadone programs is not only the morbidity of cocaine abuse itself but also the potential for infection with the human immunodeficiency virus and contracting AIDS (5). This pilot study suggests a new treatment to reduce this intravenous cocaine use. The response rate of 67% (four of six) is similar to the 63% response rate in our recent trial with desipramine in cocaine-abusing methadone patients and substantially greater than the 25% rate found among the unmedicated comparison group in that study (4). However, side effects were a significant problem for half of the patients in this pilot study. While these patients continued to take bromocriptine, compliance may be more difficult in other outpatient settings (3), and the previously successful studies of inpatients may need careful replication with outpatients (2). This pilot study is the first step in such efforts with outpatients.

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Use of Arylsulfatase A in Chronic Psychiatric Patients

Sɪʀ: Metachromatic leukodystrophy is an autosomal recessive storage disorder caused by reduced activity of the lysosomal enzyme arylsulfatase A. This leads to accumulation of nonmetabolized sulfatides in myelin and visceral organs (1). The adult form of metachromatic leukodystrophy (15%–25% of all cases) starts as a schizophrenic or paranoid psychosis (1, 2) or presenile dementia (1). The juvenile form usually starts with white matter disorders, e.g., optic nerve atrophy, spasticity, and polyneuropathy. Mahon-Haft et al. (3) reported in 1981 that metachromatic leukodystrophy was diagnosed in three of 18 psychiatric patients because of low arylsulfatase A activity in serum and leukocytes and high urinary sulfatide excretion. For diagnostic purposes, the arylsulfatase A activity in leukocytes is often determined (4). We used this method to try to replicate the findings of Mahon-Haft et al. (3).

Thirty-seven women and 22 men in two Dutch psychiatric hospitals were studied. According to *DSM-III* criteria, 53 patients had schizophrenia (disorganized, N=8; catatonic, N=2; paranoid, N=9; undifferentiated, N=17; residual, N=13; schizoaffective disorder, N=4), four had paranoia, and two suffered from primary degenerative dementia with presenile onset. The mean ± SD age of the patients was 39.4 ± 11.4 years (range=22–62 years), the mean ± SD duration of the index episode was 4.0 ± 7.6 years (range=3 weeks to 38 years), the mean ± SD total duration of the disorder was 7.7 ± 7.9 years (range=1½–38 years), and the mean ± SD number of previous hospitalizations for the disorder was 2.3 ± 3.0 (range=0–16). Blood leukocytes were isolated within 8 hours after blood sampling, and arylsulfatase A activity in leukocytes was determined by using *p*-nitrocatechol sulfate as substrate (4). The activity of arylsulfatase B and the activity of *N*-acetyl-β-ᴅ-glucosaminidase were determined for use as reference enzymes (5). Reference values were derived from leukocytes of clinically normal children and adults (N=100).

The mean ± SD values for lysosomal enzyme activity (nanomoles per hour per milligram of protein), with the reference values in parentheses, were: arylsulfatase A, 70 ± 20 (72.5 ± 18.8); *N*-acetyl-β-ᴅ-glucosaminidase, 3399 ± 1002 (3300 ± 650); and arylsulfatase B, 191 ± 75 (263 ± 89). The measured values of arylsulfatase A and both reference enzymes were all within the limits of the reference values of our laboratory (range for arylsulfatase A=34–109). No arylsulfatase A values were found in the activity range for patients with clinically proven metachromatic leukodystrophy (N=30, including five cases of the adult form; range of arylsulfatase A values=0–9). There were no statistically significant differences in enzyme activity between the patients and the control group (t=0.78). Thus, the findings of Mahon-Haft et al. (3) could not be confirmed on the grounds of arylsulfatase A activity, although more than three times the number of patients were studied. Their three patients and the majority of our patients suffered from schizophrenia. Consequently, their suggestion that metachromatic leukodystrophy is a frequently occurring disorder in psychiatric patients does not seem warranted.

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Cholinergic Mechanisms in Delirium

Sɪʀ: Two recent reports in the *Journal* by Stuart J. Eisendrath, M.D., and colleagues (1) and Ronald C. Golinger, M.D., and colleagues (2), which dealt with cholinergic mechanisms in delirium, remind the reader of a major underpinning for a significant clinical syndrome. Both studies highlighted the involvement of muscarinic receptor blockade in the etiology of delirium. It is important to note that additional mechanisms might be implicated in these and other instances of delirium.

A drug can have antimuscarinic properties without blocking the postsynaptic muscarinic receptor. The primary mechanism by which this occurs is the inhibition of the release of acetylcholine through an action on the presynaptic cholinergic neuron. Agents that have this property include dopaminergic and β-adrenergic agonists, opiate agonists, cannabinoids, barbiturates, and ethanol (3).

Further, it should be noted that some agents which seem to have presynaptic activity may act through other mechanisms as well. An example of such a drug is amoxapine, which acts as a weak postsynaptic muscarinic antagonist in vitro (4) and inhibits norepinephrine uptake in vitro, and whose withdrawal produces an atropine-responsive set of symptoms suggestive of cholinergic rebound phenomena (5). Amoxapine also induces in vivo changes suggesting supersensitivity of a central cholinergic temperature-regulating system. Amoxapine is as potent as desipramine in inducing these central anticholinergic effects (S.C. Dilsaver and R. Davidson, manuscript submitted for publication).

The variety of anticholinergic effects obtainable without direct effects on the postsynaptic muscarinic receptor has potential application in the evaluation of individuals with delirium. It suggests that the array of agents causing delirium through antagonism of cholinergic mechanisms is broader than previously thought. It offers the potential for the application of new agents and greater use of currently known agents in the treatment of delirium and may offer a route for understanding the actions of empirically used treatments for delirium.

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Survivors of Childhood Experiences in Japanese Concentration Camps

SIR: Survivors who were the child victims of Japanese concentration camps have been attending Dutch clinics in ever increasing numbers over the past few years (1). In Canada, having treated patients who were child victims of that imprisonment and having been contacted for treatment by others, I can see that these persons are presenting for psychiatric care wherever they now live. Jewish survivors who had been children during the Holocaust have received comparatively more attention in recent years (2). Nevertheless, both groups have been silent and uncomplaining, living productive lives until problems are triggered by contemporary events that remind them of their tormented past. The survivors of Japanese prison camps are unknown to most psychiatrists. I present two such cases.

> Mr. A was born in 1936 in Indonesia to a Dutch family. In 1942, the entire family was interned in a Japanese concentration camp. His father and older brother were placed in the men's section, where the father eventually died of malnutrition. Mr. A was placed with his mother and sister, and together they survived. Mr. A lived in Holland for 8 years after the war, became a writer and linguist, and actually worked in Japan for 1 year with no ill effects. He was well until 1971, when an assignment took him to the site of his camp. There was no trace of it. At that point, after 25 years of successful adaptation, he began to suffer chronic anxiety and nightmares; he was treated in Holland in the late 1970s. After a reasonable recovery, he again succumbed to illness in 1985, when he tried to write a book about children like himself.

> Ms. B was born in 1940 in Indonesia. Her parents were Dutch missionaries. At age 43 she became severely depressed following business reversals and the death of the Indonesian woman who had been her protectress in a prison camp. The woman had been a family servant. She had died in Holland, and Ms. B was unable to attend the funeral. She was overwhelmed by grief. Nightmares and preoccupations were constant from then on. Ms. B's recall of the period when she was 2½–6 years old was extremely vivid. She had observed atrocities, but adults, including physicians, told her she could not possibly have seen and/or remembered what she described. After a successful adaptation to life that had lasted more than 35 years, Ms. B decompensated following the death of the family servant who had protected her in the camp.

The precipitate illnesses of these two victims of childhood experiences in Japanese concentration camps illustrate that long intervals of apparently normal functioning can belie the presence of chronic psychological suffering. The triggers are discernible if the physician is aware that present symptoms may indeed reflect wartime trauma. Adults—even psychiatrists—do not credit survivors of childhood traumas with ability to remember. As a result, these survivors have difficulty in verifying their memories and speak about them very little.

Treatment must focus on acceptance of the patient's memories and, where these are fragmented, intrusive, and painful, on assisting the patient to structure them into an understandable sequence and meaningful context (3). Psychiatrists must be aware that survivors of World War II childhood experiences, who are now in their late 40s to mid-50s, are likely to present in increasing numbers for psychiatric care.

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Conceptual Basis of Posttraumatic Stress Disorder

Sir: The thoughtful and informed paper on posttraumatic stress disorder by Lawrence C. Kolb, M.D. (1) holds important implications for the whole of psychiatry. As Lazare (2) pointed out, clinicians use a number of tacit "conceptual models" or metatheories to comprehend the very complicated behavior and feelings of patients. Mostly broadly speaking, there are two of these models, the psychological and the biological, and both are to some degree serviceable in the understanding and treatment of mental disorders. The second of these has been increasing in prominence in psychiatry over the last 15 years.

Dr. Kolb's ideas give promise of a synthesis of these too-often polarized and antagonistic ways of thinking about clinical phenomena. Given Dr. Kolb's overall concept, is it possible that severe psychological traumas can remain operant much later in life—that they may even remain totally out of adult consciousness but leave behind permanent physical tracings etched into the structure and physiology of the mature CNS? Is this part of the reason that patients with apparently clear psychological and environmental origins for their emotional problems often respond unmistakably well to biological interventions?

At a very basic level, most psychiatrists feel, to varying degrees, that both psychological vicissitudes of human development and biological factors contribute to psychopathology, yet these two conceptual models have often seemed hopelessly divergent because one putatively deals with a theory of mind and the other with physical phenomena.

There is no a priori reason that these two scientific "paradigms"—to borrow the parlance of philosopher T.S. Kuhn (3)—cannot be reformulated into a richer and more advanced synthesis that accommodates much more data, both mental and physical, and does it in a much better way. As Kuhn suggested, this kind of saltatory reconstitution process has historically characterized many quantum jumps forward in scientific thinking. Dr. Kolb's paper shows a path in that direction for modern psychiatry.

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ROBERT J. CHIARELLO, M.D.
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Sir: I found the article by Dr. Kolb of interest because its hypothesis may account for prolonged or delayed symptoms caused by purely psychological experiences. The hypothesis is, however, based on a shifting foundation of misdiagnosis. None of five studies (1–5) showing that the majority of veterans with posttraumatic stress disorder suffer from other serious psychiatric disorders was referenced. Systematic *DSM-III* diagnoses were not made from structured or unstructured interviews. No attempt was made to exclude alcoholics and drug abusers in various stages of withdrawal, caffeine abusers, depressed patients, etc., all of whom may have excessive adrenergic activity and startle responses.

This methodological problem is so basic that it casts doubt on the theory and on the attentiveness of your peer reviewers.

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DAVID BEHAR, M.D.
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Prevalence of Panic Attacks in a Nonclinical Sample

Sir: Reports by Norton et al. (1, 2) and Barlow et al. (3) have suggested that panic attacks might be much more common than previously suspected and that persons with agoraphobia and panic disorder may represent only a subpopulation of people with panic attacks. Specifically, Norton et al. (1) found, in a questionnaire survey, that 34.4% of presumably normal university students reported one or more panic attacks in the past year and, in a related study (2), that 22.7% of students reported experiencing a panic attack within the past 3 weeks. Barlow et al. (3) interviewed 108 persons who came to an anxiety disorders research clinic and determined that approximately 83% of all the subjects reported having at least one panic attack as well as having four of the 12 symptoms necessary for a panic attack according to *DSM-III* criteria. The fact that the prevalence of panic attacks may be significantly higher than previously thought has important implications for our understanding of the spectrum of emotional reactivity in general.

As part of a questionnaire (designed primarily to investigate weeping behaviors and emotions) distributed anonymously to all employees of the Payne Whitney Psychiatric Clinic, we asked respondents whether they experienced "anxiety attacks (or panic attacks)" and "how many anxiety attacks" they had experienced during the past week. The questionnaire included an appended copy of the Brief Symptom Inventory (4), which allowed us both to verify that persons who reported experiencing panic attacks did in fact report more symptoms of panic than other respondents and to determine whether persons who reported panic attacks had other psychiatric symptom patterns (e.g., depression, phobic anxiety, anxiety, somatization, or obsessive-compulsive disorder profiles).

Of 400 questionnaires distributed, 183 (46%) were returned. One hundred twenty-two (67%) of the respondents were women, and 61 (33%) were men. The age distribution was as follows: 21–29 years of age, 31%; 30–39 years, 40%; 40–49 years, 16%; 50–59 years, 10%; and 60–69 years, 3%. Eighty-two percent of the respondents were white, 17% black, and 1% Asian. Of the 183 respondents, 43 (23%) reported having experienced panic attacks, and 18 (10%) reported having had at least one panic attack in the past week. Seventeen (40%) of the respondents who reported panic attacks met our Brief Symptom Inventory criteria for validation, compared to 10 (8%) of the 129 subjects who denied having panic attacks ($\chi^2=22.27$, df=1, p=0.0001). (All chi-squares reported in this letter have the Yates correction.) Ten (56%) of the 18 respondents who reported having a panic attack within the past week and 11 (8%) of the 140 respondents who did not met our Brief Symptom Inventory criteria for validation ($\chi^2=27.48$, df=1, p=0.0001).

Persons who reported experiencing panic attacks (as well as those who experienced panic attacks within the past week) showed no significant differences from our total sample with respect to age, sex, and race. Persons who reported panic attacks were more likely than our general sample to report substantial anxiety ($\chi^2=9.67$, df=1, p=0.002) and showed a trend toward reporting more depression ($\chi^2=2.98$, df=1, p=0.10) and more obsessive-compulsive symptoms ($\chi^2=3.16$, df=1, p=0.10). Persons who reported having panic attacks within the past week showed significantly more anxiety ($\chi^2=20.11$, df=1, p=0.0001), more depression ($\chi^2=10.20$, df=1, p=0.002), and more obsessive-compulsive symptoms ($\chi^2=8.74$, df=1, p=0.005) than our general sample of respondents.

In summary, our investigation of the prevalence of panic attacks in a nonclinical sample supports previous research. It appears that a considerable portion of the general population, probably in the range of 10%–30%, has at one time experienced a panic attack and that there is a somewhat lower prevalence of frequent panic attacks in nonclinical populations.

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SARA L. KENNEDY, M.D.
M. KATHERINE SHEAR, M.D.
New York, N.Y.

Patients' Review of Case Reports

SIR: Recently I received the last payment from a patient who had already terminated insight-oriented psychotherapy. On the back of the check was written, "Endorsement hereof shall constitute the payee's guarantee that there will be no additional compensations forthcoming to him from other sources, monetarily, professionally, or otherwise, directly or indirectly, for his work with me, and access to me and my history, neither in whole nor in part, composite or distorted, even though my identity be disguised, without the submission to me, in each and every instance, of all notes, outlines and manuscripts for review and emendation, and without a signed Release from me, or my heirs, and without suitable compensation in return."

The scientific literature about the termination process is large, but I believe this is the first time such an enjoinder by a patient has been reported (although there have been lawsuits regarding the failure to disguise a case report sufficiently, and some analysts, such as John Sours [1], have discussed the scientific difficulties with such disguising). If all patients thus enjoined their psychiatrists and reviewed their case histories prior to publication, it is interesting to speculate whether our literature would be less or more objective as it pertains to various matters of patient care.

This letter is submitted with the approval of the patient.

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DAVID V. FORREST, M.D.
New York, N.Y.

Correct Diagnosis for "Alcoholic Jealousy" in *DSM-III-R*

SIR: An apparent misprint on page 127 of the new *DSM-III-R* suggests that "alcoholic jealousy" be diagnosed as alcohol dependence and delusional disorder, persecutory type. However, accompanying alcohol dependence, the obvious and correct diagnosis—which is indicated in the index under alcohol-induced organic mental disorders—is delusional (paranoid) disorder, jealous type.

BRUCE BLOCK, M.D.
Buffalo, N.Y.

Dr. Spitzer Replies

SIR: Dr. Block and the index of *DSM-III-R* are correct in noting that the concept of "alcoholic jealousy" should be diagnosed as alcohol dependence and delusional (paranoid) disorder, jealous type. We made a mistake, and the text of *DSM-III-R* is incorrect.

ROBERT L. SPITZER, M.D.
New York, N.Y.

The Observed and the Observer

SIR: It seems that we psychiatrists (and psychologists) are prone to rush in where physicists fear to tread. Richard D. Lane, M.D., and Gary E. Schwartz, Ph.D., in "Levels of Emotional Awareness: A Cognitive-Developmental Theory and Its Application to Psychology" (1) rather lightly invoked the names of Einstein and Heisenberg as lending support to their dubious thesis that there is "no such thing as a tangible (i.e., completely measurable) objective reality."

Einstein's theory of special relativity delineates measurement of phenomena between observers in relative uniform linear motion, and the Heisenberg principle governs the inherent (though statistically predictable) uncertainty in simultaneous measurement of position and momentum of a particle. To say that these theories imply the impossibility of the correctness of a perception, whether it be physical or emotional in nature, is pure make-believe.

Of course, there is a long tradition of awareness that perception is influenced by the observer (2, 3). That does not mean that there are no objectively verifiable realities. To take the very principle under discussion, the Michelson-Morley experiment (4, p. 15–3) verified the reality of the incorrectness of Newtonian physics. Heisenberg and Einstein well understood that observation conforms to predictable and verifiable natural laws (3).

The indiscriminate misapplication of the ideas of physics to psychiatry and philosophy is part of a long and inglorious tradition stretching back at least to von Bertalanffy and systems theory. Such practices have been roundly dispatched with customary lucidity by Richard Feynman (4, p. 38–8), among others.

We can have confidence in the legitimate application of scientific principles of investigation in psychiatry. To lean on the broken crutch of a borrowed and misapplied principle from a fraternal discipline is to court disaster.

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Drs. Lane and Schwartz Reply

SIR: We wish to thank Dr. Buckingham for his letter. Unfortunately, we found it somewhat perplexing, since he attributes to us a position that we do not hold. Nowhere in our paper did we state that there is "no objectively verifiable reality." If that were the case, we would not have developed a psychological test, the Levels of Emotional Awareness Scale, to empirically test the hypotheses put forward in our paper. Rather, we invoked findings from modern physics to address fundamental issues pertaining to the process of acquisition of knowledge. As such, we addressed limitations in the scientific method, not the impossibility of obtaining anything useful from it.

The central issue is whether the act of observation inevitably influences the nature of the observations made. The work of Heisenberg and others has demonstrated at the subatomic level that as a result of the effects of observation, only probability distributions can be precisely determined, not specific events. Their demonstration of the limitations on what can be precisely measured simultaneously suggests that selectivity is necessarily involved when one conducts any experiment. Dr. Buckingham is quite correct that this does not prevent us from identifying predictable and verifiable natural laws. What it does say, however, is that no one experiment will give us the entire answer. It is in that sense that one set of observations cannot be judged absolutely correct in relation to another set of observations.

It is important to note that the nature and importance of the distortion associated with observation is a function of the relative magnitude or level of organization of the observer and that which is observed. For example, simultaneous measurement of the position and momentum of a tennis ball in flight creates uncertainties due to quantum effects only at the 34th decimal point; i.e., there is an effect that has no significance in the macroscopic world. However, the anthropologist who studies a small village isolated from modern life will alter village life simply by being present (1). Since Heisenberg himself viewed the uncertainty principle as a generic principle that was legitimately applicable to scientific domains other than physics (2), we believe that our reference to his work was well founded.

The central thesis of our paper was that one's preexisting knowledge of one's own emotional experiences affects the nature of one's subsequent emotional experiences and that these experiences are organized at five levels of differentiation and integration. In our view, this is entirely consistent with the generic principle that the act of observation alters that which is observed. Furthermore, we maintain that this psychological model may be helpful in reassessing the longstanding belief that no lawful relationship exists between the reported experience of emotion and the associated physiological response (3). It is therefore somewhat ironic that Dr. Buckingham concluded that we do not believe that such lawfulness exists.

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RICHARD D. LANE, M.D.
GARY E. SCHWARTZ, PH.D.
Chicago, Ill.

Ethical Problem Solving

SIR: Edward M. Hundert, M.D., has elegantly described the way in which a reasonable person or committee can balance opposing ethical points of view (1). Implicit in his recommendations for solving moral dilemmas is another goal: alleviating the anxiety that the arbiters could be wrong by obsessively weighing all current factors in the context of inner conscience and previous experience. This goal is relative and expedient in that it focuses on an internal need to balance conflict. Many of the most intense moral dilemmas are approached differently by the participants; the goal is not to solve an internal psychological problem but to conform an inner state of mind to an external standard that may transcend reason and be described in religious or political language.

Arguably, Dr. Hundert's critique applies well to a psychologically mature individual or group in an agnostic, calm, academically open-minded setting, who are able to tolerate a high level of diversity, and whose oxen are not being gored. He briefly mentioned more difficult settings, such as intercultural conflicts. Nowhere did he address the unavoidable mental set of many people who are loyal to absolute standards that, rightly or wrongly, do not lend themselves to trade-offs or even to cultural pluralism.

It may be easy for those of us who believe in scientific, psychiatric relativism to look at deeply held religious or political beliefs and analyze them as neurotic derivatives of childhood conflicts with authority and feelings of helplessness. But we must not allow our scientific framework to close us off from an empathic understanding of the fact that many of our patients and colleagues still feel morally wrong despite proffered rationalizations or ethics committee votes. The rational effort to balance irreconcilable viewpoints may be viewed as moral compromise, not success. Clinical expediency leads us too often to ignore the emotional experience of absolute, externally defined morality and the terror or peace it may engender. Technical neutrality does not offer a way to interpret or understand politics and religion without reducing them to pathology.

For example, our relativism in areas such as decisions about abortion can blind us to the feelings of those who oppose the act categorically on religious grounds, even as we claim it is they who misunderstand us. One of us (D.K.) recalls helping a Roman Catholic graduate student impregnated by a rapist to put aside her beliefs long enough to have an abortion and finish school; she had not balanced her conflicts so much as ignored one side of herself. One of us (2) has recommended guidelines for the dynamically trained psychiatrist in approaching conflicting opinions in general and has specifically approached the anguish inherent in the right-to-life versus prochoice issue.

We also fail to see how it helps to say, as Dr. Hundert does on page 840, that "the demand for consistency applies at the level of principles, not actions." Indeed, a consistent moral state of mind may dictate different actions at different times. However, moral principles are traditionally stated in action language, whether we look at the Ten Commandments or the Bill of Rights. Deviations from them are not excused because the individual or an examining committee "thought about it" but because they either are found "not to have occurred" (e.g., an abortion saves the mother's life and therefore is not an act of murder) or are simply judged wrong.

Dr. Hundert's work described how many modern secular institutions solve ethical problems in ways they consider open-minded. Many people and groups hold more traditional, less psychological views of morality. Ignoring these views, even if we disagree with them scientifically, may isolate us in our efforts to be of help.

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DAVID KAHN, M.D.
DAVID V. FORREST, M.D.
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Dr. Hundert Replies

SIR: In a reference in my article about ethical problem solving, J.L. Mackie (1) explained that there exist two orders of ethical judgments. First-order moral views concern the practical questions of how we ought to live our lives, whether this takes the form of leading a virtuous or religious life or trying to maximize happiness and minimize suffering. Second-order, or "metaethical," views concern the status of our first-order morality: are our moral judgments subjective opinions or are they objective or God-given truths?

Mackie noted that "first and second order views are not merely distinct but completely independent" (p. 16). This claim is counterintuitive but is nevertheless quite true. One might hold very strong first-order moral views while believing them to be simply opinions or attitudes, and one might reject all established moral norms while believing them to be God-given absolutes. Mackie warned against the danger of correctly formulating judgments on one level only to apply them incorrectly at the other.

My model for ethical problem solving is put forth to address only the practical, first-order questions we face daily in clinical practice. It can be applied equally well within the context of any second-order, or religious, view. This is important, because the balancing of values I speak of is not meant to reflect a metaethical relativism. My own second-order approach is in fact neither relativistic nor subjective, and I join Drs. Kahn and Forrest in their concern about those who would analyze deeply held religious or political beliefs as "neurotic derivatives of childhood conflicts." We must not, as Mackie warned, move from a recognition of competing values at one level to an insistence that these values have only a relativistic status at the other. Similarly, we must not move from a belief in objective level 2 judgments to a belief that any given value can have infinite weight at level 1, as the obstetrician-gynecologist in my article and Dr. Kahn's pregnant Catholic patient both discovered. As Drs. Kahn and Forrest point out, all we do when we take "thou shalt not murder" to be a level 1 absolute is force ourselves to redefine the same action in other terms—a semantic device that sidesteps the difficult balance of values that must be achieved. Even Biblical level 1 moral principles take such forms as the golden rule, which forces us to face the practical value conflicts of daily living.

Drs. Kahn and Forrest raise a crucial issue with the fact of patients whose hearts tell them of absolute, externally defined truths even as they balance conflicting values internally in their heads. The point of working toward a "reflective equilibrium" between our moral experience and our moral principles is nothing more than this very struggle to act on behalf of both our hearts and our heads. This struggle is the central challenge of ethical problem solving and the main focus of the model, which is offered to help us reach out to patients who hold any cultural or religious second-order view. I thank Drs. Kahn and Forrest for helping me clarify how the model addresses this practical, first-order moral question.

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EDWARD M. HUNDERT, M.A., M.D.
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Ethical Issues in Drug Studies

SIR: Ethical issues were raised in the article "L-Dopa Challenge and Relapse in Schizophrenia" by Michael Davidson, M.D., and associates (1). I have two concerns. First, patients were removed from their neuroleptic medicine regimens for no ostensible purpose other than for the study. As pointed out in the article, this could have been harmful to these patients. Second, and more bothersome, these patients were given L-dopa with no expectation that this medicine would in any way help them. In fact, the expectation was that it would exacerbate symptoms.

It would be useful to know whether other professionals also have qualms about the ethics of this experiment.

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FREDERICK W. ENGSTROM, M.D.
Minneapolis, Minn.

Dr. Davidson and Colleagues Reply

SIR: Our study was part of a general effort by us and other investigators to devise clinical instruments able to predict which schizophrenic patients can maintain stable remission when not taking neuroleptic drugs. Dr. Engstrom assumes that temporary removal of neuroleptic treatment from remitted, stable schizophrenic patients is invariably harmful, while he ignores the potential adverse effects of chronic neuroleptic administration.

Although it has been established beyond doubt that neuroleptic drugs are superior to placebo in maintaining remission, a considerable number of schizophrenic patients (between 14% and 70%) do not relapse at the end of 1 year of placebo administration (1). Moreover, the estimated incidence of tardive dyskinesia is about 3%–4% per year of neuroleptic exposure (1). Chronic use of neuroleptics is also associated with aggravation of deficit symptoms and, possibly, with supersensitivity psychosis. These potential adverse effects, combined with the fact that some schizophrenic patients can maintain stable remissions when no longer taking neuroleptics, have made neuroleptic discontinuation and/or symptom-targeted administration potential treatment options. Advocates of such treatment plans share our assumption that, under close monitoring, there is little risk involved with a withdrawal of neuroleptics for a substantial proportion of the schizophrenic population. Our study design called for such close monitoring and readministration of neuroleptics in the event of sustained symptom exacerbation. Indeed, Carpenter and Heinrichs (2) reported that among 40 drug-free schizophrenic patients receiving medication for brief periods of time during symptom aggravation, outcomes in terms of rehospitalization, social functioning, and persistence of symptoms were similar to those of patients who were receiving continuous medication.

The second issue brought up by Dr. Engstrom concerns the use of L-dopa as a psychotogenic agent. Although the administration of L-dopa is occasionally associated with worsening of schizophrenic symptoms, it has been documented that this worsening is transient and does not lead to sustained relapse in most schizophrenic patients (3). Furthermore, symptom exacerbation associated with the administration of amphetamines is very responsive to treatment with neuroleptics (4). Moreover, L-dopa can have a role in the treatment of some schizophrenic patients (5).

Although some patients may experience a brief worsening of symptoms when taking L-dopa, the potential availability of a test that can predict which patients will be able to maintain stable remission without taking neuroleptic drugs may have considerable therapeutic implication. Given the adverse effects of chronic use of neuroleptics, what appear to be unethical are not careful clinical investigations attempting to determine who might be able to maintain remission without the use of neuroleptics but the failure to attempt such determinations and the tendency to accept the widespread and often unnecessary long-term use of neuroleptics.

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RICHARD KEEFE, B.A.
RICHARD MOHS, PH.D.
LARRY SIEVER, M.D.
R. LINDSEY BERGMAN, B.S.
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Clonidine and Clomipramine in Obsessive-Compulsive Disorder

SIR: M.S. Lipsedge, M. Phil., and William Prothero, M.B. (1), are to be complimented for drawing attention to the use of oral clonidine in the treatment of obsessive-compulsive disorder, a common (2) and disabling disorder. They reviewed studies documenting oral clonidine's efficacy in the treatment of obsessions associated with Tourette's disorder (3) as well as case reports of its efficacy alone (4) and in combination with antidepressants (1) in obsessive-compulsive disorder. They concluded that a double-blind, placebo-controlled trial of clonidine is justified.

We have presented preliminary findings of our double-blind, placebo-controlled pharmacological challenges with intravenous clonidine (2 μg/kg) in six adult obsessive-compulsive patients (5). We reported a transient marked reduction in obsessions (81% mean decrease) in all six patients following a single infusion of intravenous clonidine; this differed significantly from behavioral ratings following placebo ($p=0.019$).

However, behavioral effects following an acute pharmacological challenge are often quite different from the chronic effects of a medication. We have not been impressed with the results in two patients treated by us with oral clonidine on a chronic basis. Nevertheless, the possibility of noradrenergic factors in the mediation of these symptoms remains, and we eagerly await the results of controlled studies of oral clonidine in obsessive-compulsive disorder.

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MICHAEL FAY, R.N.
MICHAEL R. LIEBOWITZ, M.D.
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Psychiatric Residents' Attitudes About the Internship: An Additional Variable

SIR: William Coryell, M.D., presented interesting and informative data on shifts in attitudes among psychiatric residents over 10 years (1). He cited as the strongest trend the increasing importance attached to the internship, stating, "Residents in 1986 were almost twice as likely to consider this essential to their training as were residents in 1976."

Dr. Coryell did not mention an important difference in the samples of residents that may in part have accounted for the dramatic change in the importance assigned to the internship. From 1970 until 1977, the American Board of Psychiatry and Neurology did not require an internship for Board certification (2). In effect, this presented graduating medical students with the option of obtaining a traditional internship followed by a 3-year residency or entering a 3-year residency directly from medical school without an internship. Therefore, a considerable number (perhaps as much as 40%) of Dr. Coryell's 1976, 1978, and 1980 samples would not have had an internship experience. Although no data were presented, it seems reasonable to suspect that residents who had chosen the internship would rank it essential, whereas those who chose not to take an internship would value it less. The 1986 sample, unlike the three initial groups, would have entered postgraduate training after the Board reinstituted the internship requirement and thus would have completed an internship (3). Appreciation of this sampling variable may be helpful in interpreting the significance of the "gain" in importance of the internship in Dr. Coryell's study.

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MILES K. CROWDER, M.D.
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Dr. Coryell Replies

SIR: I differ somewhat with Dr. Crowder; I suspect that residents who were *required* to complete an internship year were more likely to find that experience essential than were other residents. Although I mentioned in an earlier paper (1) the probable impact of these policy changes on attitudes, I believe this factor fails to explain the consistency of changes across all the surveys I described. Each survey polled residents in their final year of training. Since the policy change required residents who began training in July 1977 to complete an internship year, differences between 1976 and 1978 survey results should not have been influenced. Yet, the difference between these surveys in proportions of residents who advocated internships resembled the difference between the 1978 and 1980 surveys. Moreover, this increasing advocacy of medical aspects of training appeared also in the increasing percentages of residents endorsing medical education and experience in neurology. Thus, while I do not doubt that these forced experiences influenced attitudes, I believe overall patterns suggest an overriding increase in appreciation of the medical aspects of psychiatric training.

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WILLIAM CORYELL, M.D.
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Choice of a Residency Program

SIR: After finding that geography was one of the four most important factors in medical students' choice of a residency program in 1981, William H. Sledge, M.D., and associates (1) questioned whether that transitional class of students might have been different from succeeding classes. In a workshop at the January 1987 meeting of the American Association of Directors of Psychiatric Residency Training, Dr. Paul Rodenhauser discussed survey data from Ohio's residency programs which indicated that students differed from residents and faculty members in attributing more importance to various geographic factors.

To enhance recruiting procedures at the University of Michigan, we sent a very brief questionnaire to 26 applicants who did not match to our program. This group included students whom we did not rank as highly as those we matched as well as those whom we ranked higher. We had a 50% response rate. Six (46%) of the 13 respondents indicated that geographic location was a major factor in the decision. Fifty percent of this group indicated that it was the most significant factor in the decision. It is of note that almost all of them regarded our geographic location very positively, but the locations of the programs to which they were going offered particular advantages, often related to significant others or specific life style interests.

Other factors we inquired about included the orientation of the programs (ours and the ones to which they were going); educational, clinical, and research components; and their impressions of the faculty members and residents they met. Summing all of these factors, we found little difference in the assessments of the programs, although one or another specific factor played a part in the decisions of individual applicants. Consistent with the findings of Dr. Sledge and associates, clinical and educational components seemed to be more important than orientation in the students' positive assessments of the programs to which they were going.

From this very small sample, it seems that the class of 1987 did not differ substantially from the class of 1981.

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ELAINE PITT, M.D.
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Dr. Sledge and Associates Reply

SIR: While Dr. Pitt's sample is small and her results cannot be generalized with confidence, she does provide corroboration for what may be a general trend. We hope that more studies will be undertaken to help clarify the factors that applicants deem important in choosing a residency training program.

WILLIAM SLEDGE, M.D.
PHILIP J. LEAF, PH.D.
MICHAEL H. SACKS, M.D.
New Haven, Conn.

Solvent-Inhalant Abuse

SIR: In this journal, Joseph Westermeyer, M.D., Ph.D., presented his experience and reviewed the literature on solvent-inhalant abuse, including 94 references (1). Inhalant abuse is popular with the young and poor. Volatile hydrocarbons are often used as intoxicants by groups of Hispanic and American Indian preadolescents and adolescents. Inmates in detention centers sometimes use paint thinner or cleaning solvents to self-intoxicate when other drugs are unavailable.

In a survey of middle-class chemically dependent adolescents (2), Peary and I found that the most popular inhalant drug was nitrous oxide, usually contained in disposable aluminum minitanks known as whippets, which are sold as propellants for whipping cream canisters. Some instant whipped cream products also contain nitrous oxide, which can be used to self-intoxicate. Isobutyl nitrite was the second most popular inhalant-euphoriant found in our study (2). This analogue of amyl nitrite can be purchased in 12-ml bottles for about $4–$5. It is a potent vasodilating drug and produces a sensation of lightheadedness, palpitations, and pounding headache. The drug is sold for use as a room "odorizer" with names such as Rush, Bolt, and Locker Room.

Today, among younger adolescent drug abusers, sniffing butane from cigarette lighters and Freon from aerosol cans and refrigerant refills is also popular. Patients who frequently abuse inhalant drugs should be referred for a thorough evaluation by a specialist in chemical dependency. In the emergency room setting, confirmation of acute inhalant abuse requires gas chromatographic analysis of a blood specimen.

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RICHARD H. SCHWARTZ, M.D.
Vienna, Va.

Dr. Westermeyer Replies

SIR: The clinical observations by Dr. Schwartz on the East Coast are much like those here in the Midwest. Ethnic groups in which there is a high rate of adult substance abuse do seem to be at risk for volatile hydrocarbon abuse among children, preadolescents, and young adolescents. However, we have also seen sporadic cases among virtually all ethnic groups in this part of the country. The problem cannot merely be isolated as one belonging to the "minorities."

As Dr. Schwartz points out, adults are also at risk for volatile hydrocarbon abuse when other drugs of abuse (including alcohol) are not available to them. We have treated inmates of jails and prisons, who present with psychosis, progressive dementia, or acute delirium. "Street people" who have run out of resources for more expensive drugs also use this class of drugs as emergency intoxicants. This seems to be increasing, as we now see adults who have previously experimented as children or preadolescents with the volatile hydrocarbons. Later, faced with lack of access to more expensive compounds, they revert to their childhood practice of using inexpensive or readily available intoxicants in this form.

The matter of amyl and butyl nitrite abuse is also worth emphasizing. We have encountered several patients who take 20–100 "hits" a day. While the initial use is ordinarily in a context of sexual activity, inhalation of these drugs may spread to use for social relaxation and then later for relief of dysphoria, anxiety, or panic. While the nitrite inhalants are not ordinarily considered drugs of abuse, the chronic abuser has the same difficulty in discontinuing these drugs as does an alcoholic with alcohol. Especially in this era of risk of acquired immune deficiency syndrome, use of these drugs can undermine people's resolve to avoid promiscuous sexual activity, casual sex partners, or unsafe sex practices.

I completely agree with Dr. Schwartz's recommendation that patients who abuse these drugs "should be referred for a thorough evaluation by a specialist in chemical dependency." Those without in-depth knowledge, training, and experience in this disorder are apt to pass it off as merely a secondary manifestation of another disorder or a minor problem that the patient or family can manage on their own. Either alternative is rarely the case.

JOSEPH WESTERMEYER, M.D., M.P.H., PH.D.
Minneapolis, Minn.

Phenomenology and Family History of Affective Disorder in Cushing's Disease

SIR: In addition to presenting data regarding the lack of family history of affective disorder for patients with Cushing's disease, James I. Hudson, M.D., and colleagues (1) made a useful contribution to psychiatry by showing that the lifetime rate of major affective disorder in these patients is significantly higher than that which was found in a comparison group of patients with rheumatoid arthritis. This observation further bolsters the argument that the psychiatric symptoms which develop in patients with Cushing's disease have a pathogenesis over and above a nonspecific response to severe physical illness. In our own studies of the phenomenology of Cushing's syndrome, we have reported that irritability and decreased libido occur early in the course of the disease, before patients are aware of any physical problems other than a steady increase in weight (2, 3).

However, Dr. Hudson and colleagues did not note that the *DSM-III* operational criteria for major affective disorders specifically exclude patients who have an organic disorder such as Cushing's disease, and the Research Diagnostic Criteria (RDC), too, are prohibited for use when an organic disorder preexists. Thus, strictly speaking, patients with Cushing's disease cannot meet *DSM-III* criteria for a major affective disorder. Nevertheless, these patients do indeed evidence a syndrome with great similarities to that seen in major affective disorder. In our initial series of 35 consecutive patients with Cushing's syndrome studied before treatment, 100% had increased fatigue, 85% irritability, 83% impaired memory, 77% depressed mood, 69% decreased libido, and 69% middle insomnia (2, 3). It is also important to recognize that although similar in many respects to major depressive disorder, the depression seen in Cushing's syndrome does have certain distinguishing clinical characteristics. Irritability is a prominent and consistent feature. Depressed affect is often intermittent, with episodes of 1–3 days' duration, recurring very frequently at irregular intervals. Patients usually feel their best, not their worst, in the morning. Anhedonia is not prominent, nor is hopelessness (2, 3).

Dr. Hudson and colleagues suggested that their finding that the mood disorder in 85% of their sample began during or after the onset of the medical signs of Cushing's syndrome supports the hypothesis that the affective disorder may be caused by hypercortisolism per se. We agree with the importance of the role ascribed to cortisol in regulating mood. As a result of our studies of the association of mood and hormone levels in patients with Cushing's disease, one hypothesis we favor is that cortisol may act by increasing the sensitivity of the brain to elevated levels of ACTH, β-endorphin, corticotropin-releasing factor, or some as yet unidentified peptides (4, 5). However, it is likely that in Cushing's disease there are complex effects of neuropeptides and the entire spectrum of adrenal steroids, which include but are not limited to cortisol.

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MONICA N. STARKMAN, M.D.
Ann Arbor, Mich.

Dr. Know-It-All in Movie Psychiatry

Sir: As a former movie reviewer and current practicing psychiatrist, I particularly enjoyed Dr. Irving Schneider's well-written review of movie psychiatry (1). I believe, however, that there is a fourth distinct category of movie psychiatrists, Dr. Know-It-All.

The quintessential Dr. Know-It-All appears in two of the movies mentioned by Dr. Schneider, Alfred Hitchcock's *Psycho* and Brian De Palma's *Dressed to Kill.* Dr. Know-It-All fulfills the same plot function that Charlie Chan and Hercule Poirot fulfilled in mystery films: explanation. In both films Dr. Know-It-All appears in the last reel after the murderer has already been apprehended. In both films he sits in the police station patiently explaining to all concerned exactly what took place and why. In his omniscient yet matter-of-fact tone, he provides a logical, seemingly scientific rationalization for all the exciting but inexplicable events that have hitherto transpired. Furthering the psychiatrist-detective link, one can imagine the psychiatrist—as he lights his pipe, naturally—saying, "Elementary, my dear Watson."

A comedic version of Dr. Know-It-All instantaneously cures the hero's acrophobia at the climax of Mel Brooks's *High Anxiety.* In Robert Benton's *Still of the Night,* Dr. Know-It-All, the hero, is also Dr. Wonderful. As portrayed by Roy Schneider, this psychiatrist not only solves the murder mystery by interpreting Meryl Streep's dream but, in addition, reassures a patient that payment is not necessary, gets stabbed trying to save Ms. Streep, and ultimately kills the murderer.

Finally, and fittingly, in Nicholas Meyer's *Seven Percent Solution,* Dr. Know-It-All is none other than Sigmund Freud himself. As portrayed by Alan Arkin, he not only saves Sherlock Holmes from his cocaine addiction but also explains that which the world's greatest detective had found inexplicable. In the final analysis, it is Dr. Know-It-All who gets to say, "Elementary, my dear Holmes."

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ISAAC STEVEN HERSCHKOPF, M.D.
New York, N.Y.

Dr. Schneider Replies

Sir: I appreciate Dr. Herschkopf's comments on my paper and his obvious knowledge of the movies. His Dr. Know-It-All is certainly a recurrent screen type with distinct characteristics. In my reference to the psychoanalyst as "a solver of mysteries" (p. 999) and to horror films as almost always attempting to explain pathology (p. 1000), I sought, for reasons of economy, to subsume this special breed of psychiatrist under the Dr. Wonderful rubric. Of course, with the wicked wit and ambivalence about medicine of Alfred Hitchcock and his sometime disciple Brian De Palma, it is hard to tell if their Dr. Know-It-All is a Dr. Dippy or a Dr. Wonderful.

IRVING SCHNEIDER, M.D.
Chevy Chase, Md.

Too Many Psychiatrists?

Sir: Joel Yager, M.D., and Jonathan F. Borus, M.D., in their Commentary "Are We Training Too Many Psychiatrists?" (1), asserted that there is a plethora of poorly qualified psychiatrists who are not Board certified. The authors were particularly concerned about foreign medical graduates. It was implied that this group is disproportionately responsible for poor-quality care in psychiatry.

Drs. Yager and Borus acknowledged that there is a heterogeneity of practitioners in mental health care. They did not offer any evidence that psychiatrists who are not Board certified are less competent than practitioners from other disciplines who work alongside them and often interchangeably with them. According to a report published by the American Medical Association (2), 51.4% of psychiatrists are not Board certified. Twice as many non-Board-certified psychiatrists graduate from American medical schools as from foreign medical schools. However, non-Board-certified psychiatrists are outnumbered by other kinds of providers. For example, in 1983 the American Psychological Association reported that there were 44,580 clinical psychologists. The National Association of Social Workers estimates that there are currently 60,000 clinical social workers. The elimination of any subgroup of psychiatrists will not improve a state of affairs in which the majority of practitioners has had no medical training of any kind.

Drs. Yager and Borus asserted that competence in psychiatry can be measured only by formal examination. Yet there is room to doubt the validity of a process that consistently fails to recognize competence in over 50% of those examined. In disqualifying the most highly qualified providers currently available, the proposals of Drs. Yager and Borus would lead to further downward spiraling of the quality of care within mental health centers. The authors have erroneously identified psychiatrists as being at the heart of the problem.

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ALAN E. RAINESS, M.D.
Montgomery, Ala.

SIR: The solution of Dr. Joel Yager and Dr. Jonathan F. Borus to an alleged oversupply of psychiatrists is to have the Residency Review Committee "rescind the accreditation of any residency program from which more than one-third of its graduates fail to take and pass the Boards." Drs. Yager and Borus are wise and experienced psychiatric educators. They know very well that their proposal has no chance of being implemented. The Residency Review Committee has had great difficulty disaccrediting programs that are of little academic value. The process is extremely slow, and the political obstacles are formidable. When the Residency Review Committee attempts to disaccredit a training program situated in a psychiatrically underserved area, costly litigation often results.

A more practical solution to the supply and distribution of psychiatrists is the Maryland Plan. For more than a decade, the University of Maryland and the Maryland Mental Hygiene Administration have worked together to eliminate substandard psychiatric training in the state. Three autonomous state hospital training programs have been successfully integrated with that of the university, and fewer psychiatrists are being trained in Maryland. By helping the state recruit university-trained psychiatrists, the University of Maryland has contributed to the redistribution of psychiatrists from office to institutional practice. It has not been easy! These accomplishments have required university faculty to become actively involved in the politics of public psychiatry (1–3). The success of the Maryland Plan has also resulted in a more favorable position for psychiatry vis-à-vis competing mental health disciplines.

The proposal of Drs. Yager and Borus does not address the problem of distribution of psychiatrists. Many of our best training programs are situated in the areas of the country that have the highest densities of psychiatrists. Since most graduates wish to practice in the localities in which they have trained, reducing the size of some of our large, urban training programs, including the good ones, may be a partial solution to the psychiatric manpower problem.

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WALTER WEINTRAUB, M.D.
Baltimore, Md.

SIR: Drs. Yager and Borus contended that "we are training too many psychiatrists in general and far too many poorly prepared ones in particular." They offered scant evidence to support this bipartite statement. For the first part, they gave some figures that they conceded are "crude guesses," and for the second part, they simply gave a string of nonspecific, anecdotal comments: "many examiners" (percentage not given) for the American Board of Psychiatry and Neurology (ABPN) were "shocked" by the "poor performance" (undefined) of a "sizable percentage" (not given) of candidates.

The fact that Drs. Yager and Borus made such an unconvincing case for a shortfall in quality or an oversupply of psychiatrists did not deter them from wheeling out the solution for the alleged problem. They offered us that tired old remedy which has been a failure in countless countries and centuries, the police power of the state. They would withhold a government license to practice from any psychiatry resident who does not pass the specialty Board examination. No matter whether he or she performed superbly as a resident. No matter that the Board itself relies, for the oral portion, on largely subjective evaluations by examiners who see the candidate only briefly, whereas instructors from the candidate's hospital have observed the candidate for 3 years under a wide variety of conditions.

Whence cometh the authors' enormous confidence in and sanctification of the ABPN as the ultimate determiner of whether individuals who perhaps have had a lifelong fascination with and love of psychiatry and who have solid training should or should not be permitted by the legal authorities to enter the field and be judged by the public and peers on their merits?

The authors also seem to have unbounded confidence in the rationality and justness of state licensing boards. They seem not to have considered the point raised by Locke et al. (1):

> No government unit can set rational licensing standards. Standards determine the supply of doctors. As the

standards are tightened, the supply is diminished. This means higher doctor's fees for the public, which, in turn, means that some persons cannot afford treatment. How is any licensing board to weigh the better quality treatment that higher standards would supposedly promote against the damage caused by the corollary reduction in the supply? There is no moral or just way for a board to balance the harm done to one individual by the reduced supply against the (allegedly) better quality treatment a different person will receive if standards are raised.

In their haste to bring in the government, Drs. Yager and Borus did not pause to consider alternatives, e.g., the role of competition in a free marketplace as the regulator of the flow of the supply of psychiatrists. In a situation of oversupply, the less qualified would end up with less attractive positions or leave the specialty altogether and the problem would solve itself.

Any attempt to weld together subjective evaluations (Board certification) with arbitrary standards (state licensure) and to inject the force of law behind the combination is a sure prescription for loss of individual rights.

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ARTHUR S. MODE, M.D.
Falls Church, Va.

Drs. Yager and Borus Reply

SIR: Dr. Rainess correctly understands our preference for Board-certified psychiatrists. We believe that all professions have the responsibility to certify the competence of their practitioners and are pleased that the latest data now show that 56.6% of all active psychiatrists are Board certified. Furthermore, higher percentages of younger (45 years of age or less) psychiatrists have Board certification, reflecting the greater importance certification has today than in past decades (1). Contrary to Dr. Rainess's implication, we applaud the valuable contributions of foreign medical graduates to American psychiatry. We believe that their more frequent failures on the Board examinations reflect disadvantages related to language, culture, and/or training programs that often leave them poorly prepared for both the certifying examination and clinical practice.

Although it is true that the Board examinations are imperfect "safety focused" screening examinations, we believe that failure to pass them often reflects real problems. Those who decline to take these examinations or fail in repeated attempts should not be excused from objective assessment with the rationalization that the examinations are not perfect. Even better methods of intensive assessment of psychiatric competence must be devised. Although such assessments should be an ongoing element of all training programs, we do not believe that they can be left solely to training directors, whose judgments are often contaminated by service and administrative pressures.

We disagree with Dr. Rainess's assertion that we are suggesting disqualification of some of our most "highly qualified providers." We do, however, deplore a narrow-minded, chauvinistic "My profession, right or wrong!" position. Simply putting time into a training program will not automatically produce a psychiatrist who is more competent than other mental health professionals; the psychiatrist's competence must be demonstrable through an objective external evaluation. We assert that the other mental health professions similarly need to improve their training standards and competency evaluation methods.

Dr. Weintraub, a wise and experienced educator himself, correctly states that the Residency Review Committee has historically had difficulty disaccrediting programs. However, the recent tightening of training requirements may now enable the committee to do this more effectively. Dr. Weintraub's advocacy of the Maryland Plan to eliminate substandard training and improve public psychiatric services is well-taken. However, in spite of this program's proven success, few states and universities have established similar programs. We disagree that reducing urban training programs will correct the maldistribution of practitioners, since much of it exists within urban areas (2).

With respect to Dr. Mode's suggestion that the marketplace be the sole regulator of training and practice, a considerable amount of the literature indicates that many aspects of postgraduate specialty selection and practitioner distribution are poorly responsive to marketplace factors (3). Gresham's law, that bad drives out good, often applies to professions as well as economics. We strongly dispute Dr. Mode's position that neither the profession nor the government should establish competence and safety standards. If his position were taken to the extreme, *anyone* would be allowed to practice medicine. In closing, we return to our analogy: would Dr. Mode really prefer traveling on airplanes whose pilots are not certified for their flying competence?

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JOEL YAGER, M.D.
Los Angeles, Calif.
JONATHAN F. BORUS, M.D.
Boston, Mass.

Mechanism of Neuroleptic-Associated Priapism

SIR: In the letter "Priapism Associated With Concurrent Use of Thioridazine and Metoclopramide" (1), Miroslav Valek, M.D., and associates reported a complex case in which priapism appeared to be associated with the patient's concurrent treatment with thioridazine and metoclopramide, which slowly resolved while he received diphenhydramine (it was not clear whether the latter was specifically ameliorative). The authors postulated that this episode could have been caused by the combined dopamine-blocking effects of thioridazine and metoclopramide.

I wish to offer an alternative explanation, previously posited by Fishbain (2): that priapism associated with psychopharmacology may be principally related to α-adrenergic antagonism in the absence of adequate anticholinergic antagonism. This hypothesis was consistent with the fluphenazine-associated case of a patient whom Fishbain serendipitously treated with diphenhydramine, as well as with other cases he reviewed (2). It also would be consistent with the neuroleptic-associated case I reported with Kiwhang Lee (3), in which benztropine appeared to be an effective treatment.

Concerning Dr. Velek and associates' case, thioridazine (which, by itself, has been associated with priapism) is a potent α-adrenergic antagonist besides being a dopaminergic antagonist. Although metoclopramide is indeed also a dopaminergic antagonist, it is simultaneously a potent cholinergic agonist (4). If it contributed to priapism in the case reported by Dr. Velek and associates, it may have done so by overcoming thioridazine's anticholinergic action.

Dr. Velek and associates correctly noted that priapism has been associated with many dopamine-blocking neuroleptics, but these agents are also generally effective α-adrenergic antagonists. Moreover, the antidepressant trazodone, which is not a dopaminergic antagonist, is a potent α-adrenergic antagonist without significant anticholinergic activity and has been associated with priapism, as has the α-adrenergic-blocking antihypertensive prazosin. A study with dogs led Abber et al. (5) to conclude that both chlorpromazine and trazodone cause priapism through peripheral α-adrenergic blockade.

Other support for the stated hypothesis comes from the recent use of intracavernosal injections of α-adrenergic antagonists (phentolamine, phenoxybenzamine) to produce erections in impotent men and of α-adrenergic agonists (metaraminol, norepinephrine) to cause detumescence in cases of priapism. Currently, it is thought that erections occur when baseline sympathetic activity—ultimately mediated through α-adrenergic receptors—is overridden, relaxing cavernous, sinusoidal, and helicine arteriolar smooth muscle tone and resulting in decreased resistance to arterial blood flow and decreased venous drainage, since the draining veins are compressed against the tunica albuginea. The final parasympathetic neurotransmitter mediating the smooth muscle stimulation is probably a vasoactive intestinal peptide (6).

In summary, α-adrenergic antagonism strongly correlates with priapism (some end-organ β-adrenergic receptors are present also, and intra-arterial terbutaline has produced erections in dogs). There is some support for anticholinergic agents' efficacy in treating priapism, presumably through ganglionic blockade. Other smooth muscle relaxants (papaverine, hydralazine) can also cause priapism.

Since many neuroleptics have been associated with priapism, dopamine blockade certainly cannot be excluded as a possible mechanism (although animal studies suggest that dopamine autoreceptor agonists can cause erection, and dopamine blockers increase prolactin levels in man, interfering with sexual function), but a strong case for this would involve an explanatory physiological hypothesis and clinical data that could tease apart the multiple pharmacological properties of neuroleptic drugs.

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WILLIAM M. GREENBERG, M.D.
The Bronx, N.Y.

Dr. Velek and Associates Reply

SIR: We would like to comment on Dr. Greenberg's very informative letter. First, in the case we reported, penile detumescence commenced following administration of diphenhydramine and was complete within 5 days. This is the best we can do to reply to the ambiguity Dr. Greenberg pointed out. It neither proves nor excludes the ameliorative role of diphenhydramine. Second, without controlled studies it is impossible to determine which of the two agents, thioridazine or metoclopramide, was the primary cause of the priapism.

It is also difficult to determine whether other factors in addition to a strongly cholinergic agent (metoclopramide) and a dopamine-blocking agent (thioridazine) are required to cause priapism. The strongly cholinergic (parasympathetic) action of metoclopramide may have prevented, following an erection, the switch from parasympathetic to sympathetic predominance that would normally result in detumescence, thus forcing the erection to degenerate, so to speak, into priapism. It is true that the corpora cavernosa contain a profusion of adrenergic nerve fibers and α- and β-adrenergic receptors (1). It is also true, as Dr. Greenberg correctly points out, that most antipsychotic agents have peripheral α-adrenergic blocking action (2). However, it remains to be proven that their blocking potential equals that of phenoxybenzamine or that if injected into the corpora cavernosa—ideally at the concentrations one might have them in plasma—they would be as effective as phenoxybenzamine in causing full erections in both potent and impotent subjects (3). Doubtless, one would expect the cavernosal α-adrenergic system to play a fundamental and even powerful role in the delicate balance or switch from parasympathetic to sympathetic predominance required for detumescence. Fishbain (4), quoted by Dr. Greenberg, went beyond the cholinergic-adrenergic hypothesis and suggested that a third receptor, histamine, may play a crucial role in maintaining tumescence and that, therefore, the antihistaminic action of diphenhydramine resolved the priapism in the case he reported. Fishbain (4) even suggested that priapism may be as much a central as a peripheral phenomenon. We wonder whether the concomitance of acute dyskinesia and priapism in his patient—followed by resolution of both within 3 minutes of administration of diphenhydramine, 50 mg i.v.—led to his postulating that, after all, priapism might be central, as is dyskinesia.

There are ways of elucidating these central versus peripheral possibilities, and Fishbain (4) suggested some of them. Despite the remarkable insights gained in the field of genital physiology in recent years, the pathophysiology of priapism has yet to be established. Dr. Greenberg is correct that α-adrenoreceptor-blocking agents have been implicated as causing priapism (5), but until the pathophysiology of priapism is better understood, it is difficult to attribute the triggering of this condition to any single factor. It appears, then, that controlled studies, assessment of the type of priapism, penile perfusion by isotope phallography, and other modern imaging or blood flow techniques within 3 days of the onset of priapism will be required to elucidate questions of etiology and pathophysiology beyond the insight that case reports can provide. Much work remains to be done in this area.

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MIROSLAV VELEK, M.D.
GEORGIE K. STANFORD, M.D.
LUIS A. MARCO, M.D.
Mobile, Ala.

Further Examination of Extreme Haircutting and Psychosis

SIR: We read with interest the recent report by Kirk Strawn and associates (1) regarding extreme haircutting as a possible early warning signal of a psychotic decompensation. This is an observation that we have also made in a chronic psychiatric population.

We reviewed 92 patients treated at the Day Treatment Center of the Louisville Veterans' Administration Medical Center over a 2-year period. During that time 34 patients who met *DSM-III* criteria for schizophrenia required admission to the psychiatric inpatient service. This accounted for 75% of the total admissions from the Day Treatment Center. Of these 34 patients, 14 clearly displayed some form of bizarre change in hair style immediately before their hospitalization. This represents 41% of the schizophrenic patients admitted from our center. In all cases, the sudden change in appearance was noticed before any overt signs of decompensation were recognized.

Examples of the extreme haircuts of these patients ranged from shaved heads, in seven cases, to the shaving of bizarre patterns or figures in their hair, which occurred in four cases. Two other patients shaved portions of their heads but left long strands of hair in certain areas. The remainder of the patients in our study combined bizarre haircuts with unusual color changes, for example, dying their hair bright orange.

On reviewing the charts and questioning the patients about these incidents, we found that most of our patients changed their hair styles in response to commands made in auditory hallucinations. Several patients, however, described the behavior as a response to a vague feeling of not being themselves. For these patients the haircutting appeared to represent an attempt to maintain some degree of identity in response to their psychotic decompensation.

Unlike the patients studied by Mr. Strawn and associates, all of our patients met diagnostic criteria for schizophrenia. We have not observed similar behavior in patients with bipolar disorders. *DSM-III* indicates that bizarre or eccentric behavior and appearance are associated features in schizophrenia. Other traditional views of schizophrenia emphasize the deterioration in appearance and social functioning, as well as the severe regression, that takes place (2).

None of the patients we identified displayed this type of unusual alteration of physical appearance during periods of remission. Thus, it appears that these radical changes in hair style, even in the absence of other signs of deterioration, may represent early indicators of an impending psychotic decompensation.

We agree with Mr. Strawn and associates that careful attention should be paid to sudden, bizarre changes in hair styles and, by extension, to other radical changes in appearance.

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SIR: Kirk Strawn and associates reported extreme haircutting in eight patients as a manifestation of psychosis and suggested that haircutting may accompany relapse. In alerting clinicians to this unusual behavior, they wrote, "We were unable to find any documentation of extreme haircutting as a psychiatric symptom." In fact, Sweeny and Zamecnik (1) have already studied this behavior. In their report, three schizophrenic patients had shaved their heads and one had plucked out most of her eyebrows and eyelashes immediately before an act of severe self-mutilation. Sweeny and Zamecnik suggested that the patients dramatically altered their appearance to distract themselves from increasingly intense delusions and hallucinations directing them toward the mutilation. Extreme haircutting and other highly visible self-imposed physical changes therefore may predict self-mutilation among some psychotic patients. Monitoring of these signs will not only warn the clinician of possible relapse but facilitate the provision of therapy to avert potentially fatal self-mutilatory acts.

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Selection of Subjects for Study of Depression in Adolescents

SIR: Javad H. Kashani, M.D., and associates, in their fine paper on depression in adolescents (1), stated that the subjects were "systematically solicited." We believe this methodology needs a more detailed explanation, since sampling methods are crucial to the validity of epidemiological data. The authors also stated that the subjects (students) included only those who did not change age during the 5-month data collection period. Since grade placement is based on birth date, they probably excluded the youngest and oldest students in each grade.

Dr. Kashani and associates added three criteria for "caseness" in addition to *DSM-III* criteria. The first of these, "insufficient duration of symptoms," appears reasonable, since duration is a criterion in *DSM-III*. However, we take issue with their second and third criteria. With regard to the second, using the rater's clinical judgment appears to obviate the usefulness of *DSM-III* as a research tool; why use the Diagnostic Interview for Children and Adolescents and *DSM-III* criteria if the "bottom line" is a clinical opinion? At least they could have analyzed their data with and without using this criterion. The third criterion seems to mean that a student doing well at "work" (we assume schoolwork) but poorly in peer-social or family interactions would not be considered a "case." Again, data analysis with and without these subjects and further definition of "work" would be important. However, using only a research assessment instrument and operational criteria would provide uniformity of data collection across age groups and, thereby, more meaningful comparisons of prevalence rates at various ages.

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Dr. Kashani and Colleagues Reply

SIR: We have read Drs. Geller and Garrison's letter requesting a more detailed description of the sample referred to in our article. Of course, a detailed explanation of the method is preferable, but it was impossible to do this in a Brief Communication. However, the method was described in a previous article published in this journal (1).

Drs. Geller and Garrison observe that we "added three criteria for 'caseness' in addition to *DSM-III* criteria. The first of these, 'insufficient duration of symptoms,' appears reasonable, since duration is a criterion in *DSM-III.*" Drs. Geller and Garrison are correct that we required three criteria for "caseness," but insufficient duration was not a criterion. Apparently, they misunderstood what was considered a case. Contrary to their comments, the *DSM-III* criteria were a requirement for caseness. On page 932, paragraph 4, lines 4 to 7, we stated, "A 'case' was defined as an individual who met the criteria for any *DSM-III* diagnosis and who, in the clinician's judgment, was dysfunctional and needed treatment."

In regard to the question "Why use the Diagnostic Interview for Children and Adolescents and *DSM-III* criteria if the 'bottom line' is a clinical opinion?" we used them because of the criteria they propose. Additionally, *DSM-III* does not demand assessment of impairment (2). Also, other investigators studying a general population have required the presence of impairment (3).

In reference to the comment by Drs. Geller and Garrison about "work," their assumption that this refers to schoolwork is correct. If a child was doing poorly in peer-social or family interactions, depending on the severity, he or she could be considered dysfunctional.

At any rate, we thank Drs. Geller and Garrison for their interest in our work.

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Reprints of letters to the Editor are not available.

APA Council Reports

At the fall component meetings of the American Psychiatric Association in Washington, D.C., on Sept. 9–12, 1987, the APA councils heard reports from their components. Following are summaries of the activities of the councils and their components.

The Council on Aging

Gene David Cohen, M.D., Chairperson

In its first 5 years, the Council on Aging focused largely on what distinguishes geriatric psychiatry from nonmedical disciplines, and the work of its past task forces reflected that direction. However, more recently, there has been a virtual explosion of biomedical and behavioral knowledge in the field. At the same time, critical financing issues have affected the role of psychiatry in treating the elderly, and other medical disciplines have increased their efforts to become central to the treatment of the elderly. In 1988, for example, family practitioners and internists will be sitting for a special qualifications examination in geriatrics, of which a full 20% will be given over to psychiatric issues.

In part as a response to this growing "turf" issue and in part as an outgrowth of the decade-long movement within the field of geriatric psychiatry, the council's efforts have increasingly turned to better distinguishing the role of psychiatry from the roles of other medical disciplines in treating the complex set of medical needs of the elderly. We have sought to highlight psychiatry's role to practitioners, policy makers, and the public alike. The current complement of council work groups and task forces underlines the new focus of the council—a focus that increasingly has required council members and support staff to work with other APA components and offices to achieve mutual goals.

Dominating council activity in the past 2 years have been significant efforts to gain APA endorsement for the establishment by the American Board of Psychiatry and Neurology (ABPN) of a "certificate of added qualifications in geriatrics." Such a certificate, although substantially removed from the broader issue of subspecialization, would go a significant distance in demarcating the role of psychiatry in treating the seriously mentally ill elderly, a role increasingly sought by other medical practitioners.

After nearly a year of wide-ranging debate in a variety of forums, the Assembly and Board, in November and December 1987, respectively, signaled to the ABPN their endorsement of a certificate of added qualifications in geriatric psychiatry. The importance of this endorsement cannot be underestimated, not only from the perspective of the practitioner but also from the viewpoints of the policy maker and the public at large, as evidence of the role of the psychiatrist in treating the elderly. To meet the challenge posed to APA members by the establishment of such a certificate, the council has already created the Task Force on Education and Training in Geriatric Psychiatry to develop special geriatric psychiatry curricular materials for use at the residency and fellowship levels and to outline appropriate opportunities for continuing education for practicing clinicians interested in sitting for a certificate examination.

As important as this issue has been, council activities have also focused on other areas affecting psychiatric treatment of the elderly. A council work group headed by Gary Moak, M.D., has developed a layperson's guide to psychotropic drug use in the elderly; on the basis of comments by the joint Reference Committee, it is being readied for submission to a publisher. Yet another work group's efforts led to the establishment of the Task Force on the Ethnic Minority Elderly, which in 1988 will begin to examine the needs of this population in collaboration with members of the Council on National Affairs. A third work group's product—a report on the role of the psychiatrist in treating the elderly—will come before the council at its January 1988 meeting for final review.

The council has also continued its active liaison with the American Association for Geriatric Psychiatry, the National Voluntary Organization for Independent Living for the Aged (which is part of the National Council on Aging and on whose board an APA representative sits), and the International Psychogeriatric Association. In 1987, working with representatives of the American Geriatric Society, the council developed a panel presentation on substance abuse in the elderly to be given at the 1988 annual meeting of the American Geriatric Society, and members of the council continue to participate at meetings of the Gerontological Society.

As in past years, the council has sought the advice and counsel of representatives of district branch components on aging by opening its regular meeting at the time of the APA annual meeting to interested APA members. A number of the issues before the council and its components have been brought to the council's attention during those meetings and through other communications. To further enhance this communication, particularly in light of APA activity related to the ABPN certificate of added qualifications in geriatrics, the council is considering the publication and dissemination of a regular newsletter.

Members wishing to communicate with the council or to suggest subjects for its consideration are encouraged to contact Dr. Cohen through the APA Central Office and to attend the council's open meeting at the 1988 annual meeting in Montreal.

The *Task Force on Alzheimer's Disease,* Eric Cai[illegible], M.D., chairperson, has responded to a short-term charge to develop a series of statements that will be directed at public policy makers, the public, and psychiatrists and that will delineate the specific and crucial role of the psychiatrist in the management of patients with Alzheimer's disease and in the conduct of related research. A fact sheet for lay audiences has been approved by the Board of Trustees and will be published by the Division of Public Affairs as part of its fact sheet series. A pamphlet for public policy makers was also approved for publication and use by the Division of Government Relations in its legislative and educational activities. The outline of a third document, an editorial for psychiatrists, will be presented to the council for comment in early 1988, and the final document will be ready for council consideration in May.

The *Task Force on Nursing Homes and the Mentally Ill Elderly,* Benjamin Liptzin, M.D., chairperson, is preparing the final draft of its report. That document presents not only an annotated bibliography on issues affecting the mentally ill elderly in nursing homes but also makes a series of recommendations for further action that affect training, public policy, and the role of the psychiatrist in nursing home practice. Members of the task force have provided considerable consultation to the Division of Government Relations with respect to both regulatory and legislative activities affecting nursing home care and treatment of the mentally ill. The council anticipates that further work will be needed in this area—an area in which psychiatry again is striving to establish its role and the scope of that role.

Building on issues related to financing the care and treatment of patients with Alzheimer's disease, the *Task Force on Reimbursement Options and Alternatives for the Elderly Mentally Ill,* Howard H. Goldman, M.D., chairperson, has undertaken a number of activities. A task force presentation at the 1987 annual meeting provided a detailed articulation of Medicare billing practices, including the issues related to "medical management" for Alzheimer's patients. The task force is developing a broad background paper that details what constitutes an appropriate care system for the mentally ill elderly and has suggested that the Council on Economic Affairs or the Office of Economic Affairs develop a corollary document that would articulate a financing plan for this care system. The task force has suggested holding a leadership conference on these issues in late 1988.

In addition to the two new task forces already noted—the Task Force on Ethnic Minority Elderly and the Task Force on Education and Training in Geriatric Psychiatry—a third task force, to plan and develop an APA document for use at the 1991 White House Conference on Aging, will also be established in 1988.

The Council on Children, Adolescents, and Their Families

Larry B. Silver, M.D., Chairperson

The council has continued to direct its efforts toward maximizing APA's effectiveness in addressing the mental health needs of children, adolescents, and their families.

During the course of the year, two new components were activated, one task force completed its assigned charge, and another was expanded into a standing committee. Significant liaison activities continued. APA and the council were well represented at the meetings of the National Consortium for Child Mental Health Services by Dr. Henry Work. Dr. Michael Kalogerakis represented APA at the meetings called by the State Mental Health Representatives for Children and Youth to plan a conference on the mental health needs of adolescents in the juvenile justice system. Effective liaison with the Assembly and the Board of Trustees was provided by Drs. Cynthia Rose and Lawrence Hartmann, respectively. Dr. Michael Fishman's appointment to the council as consultant has allowed council members to be kept abreast of all government programs pertaining to children and adolescents. The council requested and obtained the approval of the joint Reference Committee and the Board of Trustees for APA's sponsorship of "Families and Professionals: Partners for a Change, a National Conference on Mentally Ill Children and Adolescents," which was planned by the National Alliance for the Mentally Ill and the Virginia Treatment Center for Children.

The informal caucus of child and adolescent psychiatrists (those attending the fall component meetings) was held in September. This assembly continues to serve as an important liaison, providing exchange of pertinent information about the programs of the American Academy of Child and Adolescent Psychiatry, the American Society for Adolescent Psychiatry, the National Consortium for Child Mental Health Services, and APA's child and adolescent programs.

Dr. Marcelino Amaya assumed the leadership of the *Committee on Chronically Ill and Emotionally Handicapped Children* after Dr. John Looney's appointment to the council. The book *Chronic Mental Illness in Children and Adolescents,* an outgrowth of a conference planned and implemented by the committee, is now available from American Psychiatric Press.

The Task Force on Juvenile Justice Issues was changed to the *Committee on Juvenile Justice Issues* in view of the enormity of the issues which need to be addressed and the evidence that the problems pertaining to adolescents within the juvenile justice system will not be short-lived. Concomitant with this change, Dr. William Buzogany was appointed to chair the committee. Its members have submitted a proposal for a symposium at the 1988 annual meeting; the presenters would focus on female adolescents in the juvenile justice system. Funding is being sought for the preparation of a handbook on the role of psychiatrists in the juvenile justice system. The development of the handbook will be a joint effort with representatives of other organizations concerned with adolescents in the correctional systems.

Dr. Irving Berkovitz chairs the new *Committee on Psychiatry and Mental Health in the Schools.* To allow for some success in the first year of work, the committee opted to focus on only one facet of its broad charge. Several pilot programs will be studied. Efforts are being made to determine the number and functions of psychiatrists providing services within public and private schools.

The *Committee on Family Violence and Sexual Abuse* held its first meeting in September 1987. Plans were made to develop informational books for practitioners on five areas of family violence. Dr. Sandra Kaplan, chairperson, represented APA at an AMA-sponsored conference on child pornography in October 1987.

The council received the first draft of the report on therapeutic communities from Dr. Mark Blotcky, chairperson of the *Corresponding Task Force on Confrontational Therapies.* It is anticipated that the final draft will be available for review and approval before the next annual report of the council.

The report of the Task Force on Changing Family Patterns has been published. The council is seeking authorization to search for outside funding for a second printing of *Child Custody Consultation,* a report of the Task Force on Clinical Assessment in Child Custody.

To increase communications with specific APA components, the following three members of the Council on Children, Adolescents, and Their Families were assigned to initiate and maintain ongoing communications with the following groups: for the Joint Commission on Government Relations, Lawrence Stone, M.D.; for the Joint Commission on Public Affairs, Irving Philips, M.D.; and for the Council on National Affairs, Rosalyn Inniss, M.D.

The Council on Economic Affairs

Donald J. Scherl, M.D., Chairperson

The economics of psychiatry have become increasingly complex and challenging. During 1987 the council sharpened its focus on the major fiscal issues confronting the profession. Through the existing committees and task forces on financing and marketing, prospective payment, Social Security disability insurance, psychiatrist payment, hospital-based and hospital-related psychiatric services (standards and accreditation), and quality assurance, the council is able to address a wide variety of economic issues as they affect both our members and our patients.

The council continues to foster nondiscriminatory mental health insurance coverage, to collaborate with other APA components involved in carrying out educational programs for purchasers of health insurance, to articulate and promote fair and adequate standards of practice, to oversee the development and refinement of quality assurance programs, and to identify needs and resources for data related to these tasks. Stimulated by the broad spectrum of economic issues being addressed by various APA components, the council convened a meeting of the chairpersons of those components to hear about their activities which are related to economic issues and to begin joint consultation on how these activities might be linked to maximize the efforts of all the components and, in particular, to maximize the Association's effectiveness in economic affairs. The Oversight Subcommittee of the council was also established, to provide additional member oversight of the quality assurance programs. These programs will continue to be a major focus in 1988.

In addition to the assistance provided by the Office of Psychiatric Services, the council and its components look to the Office of Economic Affairs for major technical support of their activities. The Office of Economic Affairs is engaged in three different kinds of efforts—gathering and disseminating information; special projects, including research for the various committees and task forces; and technical assistance, such as helping members to deal with issues such as alternative delivery systems. The office gathers information on psychiatric coverage and puts together information on trends and statistics. A new computer system that will make data, abstracts, articles, and other information readily available has been purchased. It will be directly accessible to members by means of computer modems. Literature reviews are being conducted currently on a variety of topics, including capitation, cost offset studies, and utilization. The office also began to produce a newsletter, *Ecofacts,* which it plans to distribute on a bimonthly basis.

Three task forces were established to broaden the scope of activities on behalf of members and to expand the scope of economic issues on which APA is proactive. These are the Task Force on Psychiatrist Payment, the Task Force on Future Trends in Private Insurance, and the Task Force on Prospective Payment Issues.

The *Task Force on Psychiatrist Payment,* Boris Astrachan, M.D., chairperson, was established in October 1986 to examine the nature of psychiatric practice, the diversity of settings, sources of income, and costs associated with various types of practice. Initial research on the economics of psychiatric practice—average income, income in various settings, income flows, payer mixes, various reimbursement practices, the ramifications of organized care settings, and so forth—is receiving its final review. The data have already been useful in raising psychiatrists' salaries in Illinois and have great potential for use elsewhere.

The task force has two goals: first, to understand the various potential mechanisms for funding a practice and their implications for psychiatrists' eventual receipt of fair fees for services delivered, and second, to determine the methods and value scales most useful in defining the activities which form current psychiatric practice. The council has asked other components and individuals to share information with this task force to supplement the data it collects.

The *Task Force on Future Trends in Private Insurance,* Robert Gibson, M.D., chairperson, was formed to monitor emerging issues in private health care insurance and examine their implications for psychiatric benefits. The task force is considering writing a white paper to describe these emerging trends and their attendant issues, assess their pros and cons, and generally educate the membership as to what might be expected from such trends. Potential topics include advances in diagnosis and the conceptualization of disease classification systems; various outcome studies with results that might influence insurers; the impact of the utilization review, peer review, and quality assurance movements; and medical management issues.

The *Task Force on Prospective Payment Issues,* Joseph T. English, M.D., chairperson, has continued its monitoring of prospective payment issues and exploration of potential alternative payment mechanisms. A series of studies contracted by the task force has been completed and will be enormously useful because of the documentation it provides in such areas as coverage of disabilities under Medicare, the effects on hospitals of changes in the federal diagnosis-related group (DRG) system, and the impact of DRGs on minority populations. The Health Care Financing Administration (HCFA) has contracted with NIMH for a series of studies regarding improvement of the DRGs and better ways to reimburse hospitals under a prospective payment system. The HCFA is also considering contracting with the Rand Corporation to conduct a reabstracting study for psychiatry DRGs. Securing representation on the Rand or other advisory committee reviewing proposed new DRGs is of key importance to APA. Finally, the task force continues to monitor federal legislative and administrative activities related to prospective payment for psychiatry.

The *Committee on Financing and Marketing,* Howard Gurevitz, M.D., chairperson, focused most of its efforts on the National Education Project. This project used a marketing approach to assist district branches and individual practitioners in confronting the erosion of psychiatric benefits and promoting the involvement of psychiatrists in health care policy making. The project benefits APA members nationwide, providing not only technical assistance but information, materials, and detailed "how-to" strategy manuals. Because of the December 1987 expiration of the consulting contract with GLS Associates, the committee has been reviewing which activities can and should be maintained, which can be handled in-house, and which should be delegated to outside consultants.

The *Task Force on Social Security Income/Social Security Disability Insurance,* Arthur Meyerson, M.D., chairperson, addressed several major issues. Through the focused efforts of membership and staff, the guidelines for funding partial hospitalization under Medicare were rewritten to be more inclusive. The HCFA originally wrote the guidelines to exclude coverage for partial hospitalization, and the revisions have enabled such coverage in a number of states. In addition, a draft of the new regulations for partial hospitalization, to be submitted by the American Partial Hospitalization Association to the HCFA and to appropriate Congressional committees, was reviewed and amended to focus on both the need for psychiatric involvement in leadership and the need for hospital backup for all programs.

A preliminary draft of the findings of the Social Security research project being conducted by APA indicates a very high degree of reliability (above 96%) in the cases identified as appropriately documented and otherwise amenable to evaluation. In addition, findings on the degree of difficulty in evaluating cases, rated independently from the actual disability determination, could, with appropriate analysis, indicate to the Social Security Administration the categories of cases that are particularly vulnerable to poor decision making.

APA also organized a presentation for the 1987 annual meeting on disability, in conjunction with the Social Security Administration. In light of overwhelming membership interest, the presentation will be cosponsored by the task force and the Social Security Administration at the 1988 annual meeting in Montreal.

The *Committee on Interprofessional Affairs,* Mildred Mitchell-Bateman, M.D., chairperson, hosted the Sixth Annual Leadership Conference of the Joint Commission on Interprofessional Affairs in April. This commission is a consortium of representatives of APA, the American Psychological Association, the American Nurses' Association, and the National Association of Social Workers. Two elected officers and the executive director of each of the four organizations attend the annual leadership conference. In addition, the four executive directors meet quarterly to discuss issues of mutual concern.

The Joint Commission on Interprofessional Affairs is working on two major initiatives: the stimulation of counterpart organizations at the state level and the development of a consumer-oriented publication on mental health services to be offered by these four mental health care providers. APA's Committee on Interprofessional Affairs, in consultation with representatives of numerous APA components, is striving to better define psychiatric practice.

The *Committee on Quality Assurance,* George Wilson, M.D., chairperson, has been particularly active during the past year. In January 1986 the report of the Commission on Peer Review was referred to the council. The council agreed that the commission's report was valuable because it expressed specific concerns of the Assembly and assisted the council in examining the quality assurance operation, which led to some restructuring of quality assurance activities and to the creation of a council oversight subcommittee to provide additional member review of quality assurance programs. Under the council's supervision, the committee prepared a point-by-point response to the report of the Commission on Peer Review. The committee also developed a detailed mission statement. Both documents were accepted by the Assembly.

The Office of Quality Assurance has expanded in scope and responsibility, and the committee has devised a new structure to maintain appropriate governance and accountability. Six subcommittees were created: Executive, CHAMPUS, Commercial, Credentials and Training, Research and Education, and Disability. The function of the Executive Subcommittee is to provide interim governance over the Office of Quality Assurance during months in which the Committee on Quality Assurance as a whole does not meet. The CHAMPUS Subcommittee monitors the implementation of the current CHAMPUS contract, evaluates the prospects for future CHAMPUS contracts, revises the current CHAMPUS forms, and monitors proposed changes in the CHAMPUS reimbursement system. The Commercial Subcommittee examines APA's role in peer review for commercial enterprises. Commercial review is retrospective and thus has a limited usefulness, but there is a niche for such a program, particularly in difficult cases and appeals. The Credentials and Training Subcommittee will review the mechanisms whereby peer reviewers are chosen, attempt to develop a system for quality monitoring of all reviews, and develop a mechanism for periodic review of performance and for regular recertification of all reviewers. The Research and Education Subcommittee will evaluate the overall performance of APA's peer review programs, assess the impact of utilization review on psychiatrists, patients, and third-party payers, and inform APA members and the general public regarding these issues. The Disability Subcommittee will explore the possibility of offering review services to insurance companies or other fiscal third parties that insure for long-term disability.

A proposal to establish a disability claims review program with the Paul Revere Insurance Group is under consideration. Such an initiative would help to reverse the trend of insurers toward withdrawing or reducing such benefits. If the project goes forward, the committee will 1) design a suitable claim form for psychiatric disability assessment and a supplementary claim form to provide additional data regarding psychiatric disability, 2) form a panel of specialists with disability experience to provide physician reviews and training, 3) devise underwriting forms and contractual modifications to invoke certain mechanisms that will be used in the review program, 4) develop education and training materials, and 5) develop a case management system.

The committee has proposed that the peer review manual be revised extensively and expanded to encompass the movement toward preauthorization review.

In fulfillment of its commitment under the Intracorp contract, APA opened regional offices in Atlanta and Anaheim. There has been consideration of extending the current Intracorp inpatient review program to include outpatient review. Under the proposed arrangement, APA would develop screening guidelines for a computer-based review system using criteria developed in 1986, develop review procedures and policies, and provide the second- and third-level professional reviews. In addition, APA would train and provide oversight of Intracorp's staff of first-level reviewers. Recruitment problems for peer review remain a concern because of the shortage of qualified practitioners.

APA's involvement with CHAMPUS has been substantially reduced as a result of its intervention on behalf of the membership. The committee was successful in promoting a change in the maximum time allowed for reporting from 8 to 24 days, thereby giving the psychiatrist more time for assessment. Such action, however, significantly reduced the number of cases referred to APA for review and effectively reduced its income from the project.

The *Committee on Hospital-Based or Hospital-Related Psychiatric Services,* Gerald Flamm, M.D., chairperson, reviewed a number of proposed changes in the standards of the newly renamed Joint Commission on Accreditation of Healthcare Organizations (JCAHCO). Of particular significance was the committee's active involvement in shaping the JCAHCO's eligibility criteria and standards for a tailored survey of specialized programs and units for chronically mentally ill and forensic patients.

The Council on Internal Organization

Ronald A. Shellow, M.D., Chairperson

The council monitors and represents the membership by overseeing "all those matters involved in the organizational structure of the Association not covered by constitutional committees." There are 11 components that report directly to this council and 16 components that report to committees under the council. As a result, the council oversees a wide range of activities, such as program content, exhibits, and arrangements for the annual meeting; advertising policies of the Association; data processing, telecommunications, and other information systems within the Association; benefits offered to APA members, such as the legal consultation plan, retirement programs, and life, accident, and health insurance plans; the various prizes and awards presented by the Association for outstanding achievement; all personnel and staff benefit programs; and the federation of auxiliary organizations. The following items are highlights of the activities of the council and its components over the past year.

The *Scientific Program Committee,* Robert Hales, M.D., chairperson, reported that the 1987 annual meeting in Chicago was a success in terms of attendance, program quality, and income. The council has asked that the Association's budget include adequate funding for a day-care program for the children of members attending the meeting, a service that has proved to be popular over the past few years. The 1988 meeting in Montreal will be Dr. Hales's last meeting as chairperson of the Scientific Program Committee. The council has expressed its thanks for his untiring and successful efforts on the Association's behalf over the past 7 years as a member and as chairperson of the committee. Allan Tasman, M.D., will take over as chairperson after the Montreal meeting.

The *Committee on Advertisers and Exhibitors,* Henry Work, M.D., chairperson, reported that the presentation of exhibits at the 1987 annual meeting went well, reflecting the changes in hours and policy which the committee had proposed. The council has recommended that the *Committee on Advertising,* Will Strathmann, M.D., chairperson, be reorganized as a subcommittee of the Committee on Advertisers and Exhibitors to facilitate coordination between advertising in publications and exhibiting at the annual meeting and to coordinate a review of all the current policies and guidelines governing these activities.

Alan Levenson, M.D., APA Treasurer, is chairperson of the *Committee on Grants and Awards.* The committee has worked diligently over the past few years to refine the policies governing the awards and to secure adequate funding to ensure the longevity of these prestigious awards. In the past year, the committee recommended approval of the Kempf Fund Award for Research Development in Psychobiological Psychiatry, a significant award that will honor the work of a senior researcher and support the education of a research trainee. In addition, the committee has worked with the chairpersons of the award boards in an effort to secure appropriate funding and has studied some proposals for new awards.

The *Personnel Committee,* William Sorum, M.D., chairperson, has completed work on a revision of the personnel policies and procedures manual and has directed attention to improving the functioning of the staff retirement plan.

The *Committee on History and Library,* Lucy Ozarin, M.D., chairperson, has been actively preparing a presentation for the 1988 annual meeting, giving input into the "Profiles in Psychiatry" series, arranging for the transcription of tapes from the Association's oral histories collection, helping to set up the new Kenworthy Learning Center, and improving the importance and functioning of the APA Library.

The *Committee on Information Systems,* Wandal Winn, M.D., chairperson, reported on the continuing improvement in the Association's computer system, which is being expanded to be available to members and district branches. Its *Subcommittee on Telemedical Services,* Jane Preston, M.D., chairperson, continues to look into the applications and the legal/ethical implications of offering medical services through telecommunications.

The *Committee on Special Benefit Programs,* Abram Hostetter, M.D., chairperson, has arranged for improved communication for participants in the legal consultation plan. The committee plans to continue to offer seminars on tax reduction and office automation, begin seminars on careers in clinical practice, and work on a new program for members that will offer retirement planning services.

The *Committee on Friends of the APA,* Cynthia Rose, M.D., chairperson, has completed work on bylaws for the Federation of APA Friends, an umbrella organization for groups who wish to assist with the work of the Association. The APA Auxiliary is the first such group.

The council, in cooperation with the Joint Commission on Government Relations, looked into the implications for the Association of proposed changes in the tax laws. It also investigated methods of improving communication between members and the corporations that handle APA's insurance-related matters and of increasing the members' input into insurance programs.

In summary, the Council on Internal Organization continues to represent the members in the business and internal workings of the Association. It welcomes all input and comments from members.

The Council on International Affairs

Harold Visotsky, M.D., Chairperson

As the primary component responsible for the Association's international activities, the council works closely with the Office of International Affairs in coordinating activities involving aspects of psychiatry that have international implications. In addition to overseeing and assisting in the work of components reporting to the council outlined later in this report, the council and office serve as a clearinghouse for referrals and contacts for APA members and colleagues abroad. A number of APA members have benefited from this consultation, and assistance has been sought by colleagues from many other countries, including Austria, Argentina, Australia, New Zealand, Brazil, Bulgaria, the People's Republic of China, South Korea, West Germany, Poland, England, East Germany, Kenya, Nigeria, Senegal, Venezuela, Uruguay, Canada, Chile, Finland, Japan, Spain, Honduras, Iceland, Guatemala, Norway, Egypt, Hong Kong, Lebanon, Mexico, the Soviet Union, South Africa, India, the Netherlands, Denmark, Peru, Greece, Belgium, Switzerland, Yugoslavia, Sri Lanka, Sweden, Scotland, and Pakistan.

The council is concerned that (at this writing) APA's "Statement of Mission, Goals and Objectives" has no international focus. The council believes that APA has an obligation to the community of nations to address this issue in a concrete way that will facilitate exchange of knowledge between APA and associations in other countries. Thus, the council suggested wording to be included in the statement that should address this oversight.

This year the council has addressed a number of issues regarding the World Psychiatric Association (WPA), including APA's response to a questionnaire sent out by a working group that is proposing a restructuring of the WPA. The council continues to ensure that APA is responsive to international organizations so the American perspective can be present in various initiatives. In the upcoming year, the council will focus on a number of issues regarding the WPA in order to advise the Board of Trustees as to what actions need to be addressed before the VIII World Congress of Psychiatry, which will be held during October 1989 in Athens, Greece.

The council continues to be involved in the International Scholars Program for the APA annual meeting and appreciates the initiative shown by the Scientific Program Committee in its support of this successful series of lectures. The council was particularly pleased to have the participation of Dr. Anatoly Koryagin in the 1987 annual meeting only 3 months after he was released from prison in the

Soviet Union and just 1 month after he immigrated to the West. This was a highlight of the annual meeting. Dr. Koryagin has agreed to also attend the 1988 annual meeting. The other International Scholars this year will be Dr. Franco Ferracuti of Italy, Dr. Serge Lebovici of France, Sir Martin Roth of Great Britain, and Dr. Jules Angst of Switzerland.

Through the initiative of the council and the Office of International Affairs, the APA Board of Trustees approved in principle negotiations with authorities of the Soviet Union to allow an APA delegation to visit that country to see specific patients and hospitals. In addition, APA has offered to facilitate a similar visit by Soviet psychiatrists who wish to come to the United States. The Soviet Foreign Ministry and Soviet psychiatrists have invited a number of individuals and organizations to send delegations to the Soviet Union to see for themselves whether or not there are actual abuses of psychiatry in that country. Unfortunately, they have not yet issued such an invitation to the APA even though they are aware that it would probably be accepted. A number of other organizations, including some associated with the U.S. government, believe that it would be more appropriate for APA to send a delegation of psychiatrists, but as of this writing the Soviet authorities have not yet responded.

The *Task Force on Terrorism,* Louis J. West, M.D., chairperson, has organized an outstanding symposium for the 1988 annual meeting in Montreal. It will focus on the many functions psychiatrists perform in times of terrorist activities, e.g., treatment of individual victims and their families and consultation to individuals and agencies who must negotiate with terrorists and to those who must engage in long-range planning to cope with the threat of terrorism. The task force is aware that the media often seek advice or commentary from psychiatrists to illuminate terrorist-related events, and a list of competent and knowledgeable spokespersons is being assembled and will be shared with the APA Office of Public Affairs. In addition, the task force is working on a white paper that will provide background on terrorism, suggested readings, and clarification of the issues; publication of this work will be considered.

The *Task Force on Problems of Americans Overseas,* Eric Plaut, M.D., chairperson, has decided that it is not practical for APA to take a major lead in the study of problems of Americans overseas but, instead, would like to provide psychiatric consultation for a similar project taken on by another organization. The task force is planning to hold a small meeting with executive officers of major organizations employing large numbers of Americans who live and work abroad to discuss the possibilities for future collaboration. In addition, the task force has approached American Psychiatric Press in order to ascertain its interest in producing standardized training materials and videotapes for Americans who plan to live and work abroad. The task force is exploring with other organizations the feasibility of sponsoring and funding workshops to deal with cross-cultural problems that arise when Americans go abroad for long periods of time and when individuals from other countries come to live in the United States. Finally, the task force is working on an article addressing these problems, which it would like to see published in *Hospital & Community Psychiatry.*

The *Committee on International Abuse of Psychiatry and Psychiatrists,* Michael Zales, M.D., chairperson, continues to have conference calls once a month to deal with the large volume of materials sent to it from APA members and from outside organizations and individuals. The committee is heartened by the many changes pertaining to patients' rights that are occurring in the Soviet Union. However, there are still concrete reasons for concern over the use of psychiatry for political purposes in that country and concerns over how to influence the opinions of Soviet psychiatrists, who will be called on to address these issues. Formal contact with our Soviet colleagues almost always involves Soviet leaders, and it is difficult to communicate and collaborate with psychiatrists, who do not have such power and authority. There is strong evidence that dissidents are still being put into mental hospitals in that country, but it is hoped that laws will soon be passed to aid such victims. The committee continues to respond to referrals from a variety of countries, but the most systematic abuse continues to be in the Soviet Union.

The Committee on International Abuse of Psychiatry and Psychiatrists has done a survey of the human rights activities of over 200 allied organizations to ascertain if they have positions on psychiatric abuse. The committee plans to submit a proposal for a symposium for the program of the WPA Regional Symposium to be held in Washington, D.C., in October 1988. The purpose of this symposium would be to take a positive approach by discussing scientific aspects of psychiatry and bringing in human rights and abuse issues as appropriate.

The committee has established several liaison relationships with other APA components that have proven useful. One committee member sits in on meetings of the Committee on Human Rights, and another attends meetings of the Committee on Abuse and Misuse of Psychiatry in the United States. The Committee on International Abuse of Psychiatry and Psychiatrists continues to circulate a videotape on psychiatric abuse issues that was prepared last year, and it has recently arranged for a tape to be made of a speech given by Dr. Anatoly Koryagin. These tapes can be borrowed from the Office of International Affairs.

The *Committee on Human Rights,* Lawrence Hartmann, M.D., chairperson, is looking at APA position statements that deal with human rights issues with the intent of updating and revising those which are out-of-date and no longer relevant. The committee also is trying to motivate other organizations, particularly the American Medical Association, to become more involved in human rights issues. This would be particularly helpful to the individuals and organizations in various countries who put themselves at great risk because of their human rights activities. This is particularly true of the Medical Association of Chile, which is very active in the investigation of physicians' roles in torture. The president, secretary general, and other officers of that association have been detained and imprisoned at various times because of these activities.

The committee has been working with the American Association for the Advancement of Science (AAAS) in obtaining APA cosponsorship of a human rights mission to South Africa in April 1988. Major funding for this mission will be provided by a grant given to the AAAS, but APA is particularly interested in sending an additional psychiatrist who went on the APA mission to South Africa in 1978 and who could witness any improvements or lack thereof since the previous mission. There have been reports of great improvements in the psychiatric care of members of all races in South Africa, but there have also been dissenting opinions to these reports. The committee is beginning to work with the Center for Victims of Torture in Minneapolis on specific problems encountered by torture victims who move to the United States. One such problem is denial of insurance reimbursement for treatment because torture is often considered a preexisting condition. The committee is looking into possible roles for APA in assisting this center and others that may develop in this country to treat the many individuals who come to the United States for assistance.

The *Task Force on International Education,* Normund Wong, M.D., chairperson, has been attempting to establish a program to help midcareer psychiatrists from other countries come to the United States for 6 months to 3 years of training in specific areas of psychiatry and return to their home countries to impart the knowledge gained during this study time. To this end, the task force has sent out questionnaires to all training centers in the United States, to all major psychiatric organizations in other countries, and to all APA Corresponding Members and Fellows. The task force and council have been gratified by the results of these questionnaires and the high level of interest in the program in the United States and abroad. However, it may be difficult to accomplish all that is hoped for with the existing staff and financial resources allocated to this project. Thus, the task force has devised a list of options to discuss with the council, the joint Reference Committee, and the Board of Trustees, and the decision on future activity is now in the hands of the APA leadership. The task force will carry out the options designated. It is hoped that APA will be able to take part in the American Medical Association's International Medical Scholars program and programs being designed by the Educational Commission for Foreign Medical Graduates.

The *Task Force to Plan the World Psychiatric Association Regional Symposium,* Robert Hales, M.D., chairperson, has been working hard on this congress, which will be held Oct. 13–16, 1988, in Washington, D.C. A "Call for Papers," which includes basic program information, submission forms, registration forms, and hotel reservation information, is available from the Office of International Affairs. The program will begin with "An Update From NIMH" and will be followed by the invited symposia "Affective and Anxiety Disorders," "Schizophrenic and Organic Disorders," and "Towards an Integration of Nomenclature in Psychiatry." The opening and closing sessions will feature lectures by Dr. Gerald Klerman and Sir Martin Roth, respectively. The other formats will include symposia, individual papers, and poster sessions. An outstanding social program is also being planned to facilitate more informal communication among participants.

The *Task Force to Plan the Joint Meeting in China,* Herbert Pardes, M.D., chairperson, has been making arrangements for this conference, which is being cosponsored by the Chinese Medical Association and will be held in Beijing, Aug. 14–18, 1988. An excellent travel package is available which has been arranged by the Office of International Affairs and the Chinese Medical Association and includes various optional tours in China. The scientific program, which has been worked out in conjunction with our Chinese colleagues, will include speakers on advances in biological psychiatry, advances in child psychiatry with special attention to the one-child family, tissue transplantation, epidemiology, new concepts in genetics in psychiatry, schizophrenia, disorders of the elderly, psychosocial factors in stress, diagnostic classification, psychotherapy, primary health care and psychiatry, substance abuse in adolescents, community mental health care, new concepts of depression and anxiety disorders, Chinese traditional medicine, transcultural psychiatry, forensic psychiatry, psychiatric education and continuing medical education, and rehabilitation. Further information about the meeting in China can be obtained from the APA Office of International Affairs.

The *Task Force on the Psychological Aspects of the Middle East Peace Process,* George Tarjan, M.D., chairperson, is attempting to raise funding for the project "Role of Education in the Peace Process." The task force continues to maintain contacts with individuals in the Middle East who are committed to this project and to have small planning meetings when these individuals visit the United States for other purposes. There is a renewed possibility of funding at present, and letters of support from our Middle Eastern participants are being accumulated to show widespread support for the project in that area of the world. The task force still has a challenge grant from the U.S. Institute for Peace but cannot use the funds until additional support is obtained. In the meantime, the council has taken over the main responsibility for this project, under the direction of the council's vice-chairperson, Dr. Tarjan, and a new task force will be appointed when funding is secured.

The *InterAmerican Council of Psychiatric Associations,* Evaristo Gomez, M.D., APA delegate, has been instrumental in facilitating various events during international meetings in Latin America and at the APA annual meeting last year in Chicago. The council, however, is exploring other possibilities for collaboration with organizations in the Americas and may attempt to establish links between them and complementary groups in the United States, such as the American Association for Hispanic Psychiatrists and Black Psychiatrists of America, so that APA could assist these working relationships at designated times but activities could be conducted independently from the InterAmerican Council. Various options for structuring the InterAmerican Council have been explored with the hope of increasing organizational membership, but there has not been much success. The Office of International Affairs continues to maintain ties with many psychiatrists in the Americas, and the debate continues on whether there is a need for a formal structure such as the InterAmerican Council.

The Council on Medical Education and Career Development

Robert L. Williams, M.D., Chairperson

The primary responsibility of the council is to provide medical education to psychiatrists and physicians in other fields. As part of this function, the council provides recommendations to APA and its joint Reference Committee on psychiatric education for medical students, for residents in psychiatry, and for practicing psychiatrists. Recruitment of high-quality medical students into psychiatry and the career development of psychiatrists are major functions of this council. The council comprises 17 components, each of which presents issues related to psychiatric education and career development for consideration by the council as a whole. When appropriate, the council may then refer issues to the joint Reference Committee, the Assembly, and the Board of Trustees.

1. *National Residency Matching Program.* The council, the American Association of Chairmen of Departments of Psychiatry, and the American Association of Directors of Psychiatric Residency Training have met to offer suggestions for improving the National Residency Matching Program. As of 1988, all psychiatry residency programs in the nation will participate in and comply with the new match, which permits the simultaneous matching of all U.S. senior medical students into postgraduate year 1 and 2 positions in psychiatry. All dates and procedures are determined by the National Residency Matching Program. The 1988 deadline for submission of rank order lists is Feb. 19, 1988, and the match results will be released March 23, 1988. These dates extend the match process an additional 6 weeks beyond the periods in previous years. The Psychiatry Residency Match Review Board was established to adjudicate difficulties encountered by residency candidates and programs in implementing the planned match procedures.

2. *Subspecialization.* In a proposal to the council, the American Board of Psychiatry and Neurology (ABPN) identified three psychiatric disciplines it considered to have potential for subspecialization credentials: drug and alcohol abuse, forensic psychiatry, and geriatric psychiatry. The American Board of Medical Specialties has designated two types of specialty certificates: 1) a certificate of "special qualifications," which requires 2 or 3 years of postresidency training and emphasizes a distinct and separate area of practice, and 2) a certificate of "added qualifications" in a subspecialty, which designates an enhancement of or addition to the general specialty certificate. The council discussed the ABPN proposal but reached no conclusions, preferring to await a report from the APA Board of Trustees Ad Hoc Committee on Subspecialization. The council did conclude that there should be a mechanism for establishing fellowship standards in a manner similar to that for residency programs. Further, the council decided to encourage APA to take a leadership role in reviewing the spectrum of psychiatric fellowships, developing an inventory of fellowships, recommending an organized approach for the standardization of requirements, and exploring mechanisms for granting credentials and setting standards for accreditation of fellowship programs. In September, the council recommended the establishment of a task force on postresidency fellowships to address the aforementioned fellowship issues.

3. *Disclosure of psychiatric treatment.* There have been reports

that some state licensing boards and graduate and undergraduate training institutions investigate psychiatric history more deeply than medical history in a physician's or trainee's application for a license or acceptance into a training program. It was the consensus of the council that this practice might affect a physician's or trainee's willingness to seek needed psychiatric treatment. This would be especially true if it were known there was a possibility of later disclosure of confidential information that might result in the rejection of the physician's future application. The council recommended that APA appoint a task force on disclosure to address all issues of disclosure.

4. *Directory of Psychiatry Residency Training Programs.* The fourth edition of the *Directory of Psychiatry Residency Training Programs* is being distributed. The 1988 directory contains a separate section on child psychiatry training programs and a list of available postresidency fellowship programs.

The *Committee on Administrative Psychiatry,* Stephen L. Rachlin, M.D., chairperson, administered the examination for certification in administrative psychiatry in May 1987. Twenty-three people took the examination; 11 passed, seven conditioned, and five failed. The committee revised and rewrote the oral and written examinations. The committee decided that applications for the 1989 examination cycle would be due Aug. 1, 1988. This will allow the candidates' qualifications to be reviewed during the September 1988 meeting. The examination should be given Jan. 9, 1989 (rather than in February) so that the candidates can be notified by February 1 of their success or failure. The committee anticipates giving only one written and one oral examination. The regulations for the oral and written examinations will be revised.

The *Committee on Medical Student Education,* Gerald A. Melchiode, M.D., chairperson, conducted efforts to improve recruitment of medical students into psychiatry through the use of information booths at the annual meetings of the American Medical Student Association and the Student National Medical Association. The committee strengthened its liaisons with these two organizations and participated in some of their regional meetings. Dr. Melchiode reported that there are 661 APA Medical Student members and 5,221 Members-in-Training. The committee submitted the final draft of the brochure "The Resident as a Teacher" and is exploring production costs and procedures for the creation of an audiovisual tape addressing career issues in psychiatry. Work continues on the proposed award for excellence in medical student teaching.

The *Committee on Graduate Education,* Stefan Stein, M.D., chairperson, has been working with the Psychiatry Residency Match Review Board, established to monitor compliance with the National Residency Matching Program (described earlier in this report). Noting that the first year of residency is the most stressful year, the committee is compiling information on shared residency positions and is identifying ways to better integrate first-year residents into the programs. Dr. Stein continues to serve on the Association of American Medical Colleges Committee on Physician Manpower and Subcommittee on Implications of Physician Supply Issues for Resident and Fellow Education, which are developing new models for undergraduate and graduate medical education that are more consistent with present and evolving medical practice patterns. The committee urged, with the council's support, that APA recommend to the Residency Review Committee for Psychiatry that the *Special Requirements for Residency Training in Psychiatry* ("Essentials") include a written policy on parental leave. The development of a national data base of resident clinical experiences, based on the various log books now being used by a few residency programs, is being considered. These logs comply with the new Residency Review Committee requirement that training programs maintain records of the types of patients seen by residents. The Council on Graduate Medical Education of the U.S. Department of Health and Human Services (DHHS) has been holding hearings about future directions in financing, manpower planning, and priorities for graduate medical education. APA has testified at hearings of the DHHS Subcommittee on Foreign Medical Graduates and Council on Graduate Medical Education concerning the constant shortage of psychiatrists and the need to provide appropriate support for the training of future psychiatrists.

The *Committee on Continuing Education,* John W. Goethe, M.D., chairperson, reported that the Association for Academic Psychiatry/APA Regional Videotape Library continues to grow and additional teaching tapes need to be made to keep the library up-to-date. The development of model postgraduate institutes was discussed extensively, and several proposals were submitted to the council for its consideration. The committee is reviewing all current continuing education topics being addressed by APA. The committee is increasing its exploration of methods for more effective interaction with the APA Scientific Program Committee and the Institute on Hospital & Community Psychiatry Program Committee. The committee is collecting and analyzing information to identify potential directions for continuing education.

The *Committee on Consultation-Liaison Psychiatry and Primary Care Education,* Troy L. Thompson, M.D., chairperson, explored the issues of special and/or added qualifications in psychiatric subspecialties and urged APA to recommend to the ABPN that any geriatric fellowship include a substantial amount of consultation-liaison experience. The committee worked with the Boots Pharmaceuticals/APA Medical Colleagues Interactive Workshops on Depression. The members of the committee worked informally with members of the American Academy of Family Physicians to introduce psychiatrists into the arena of teaching and consulting in family medicine training programs. There was a similar interaction with the Society of Teachers of Family Medicine, which has a committee dealing with psychiatric teaching about aging and other geriatric issues.

The *Committee on the Impaired Physician,* Stephen Scheiber, M.D., chairperson, reported that the Robert E. Jones Assistance Fund has met the legal and fiscal conditions recommended by APA and that the fund will be administered by the APA Auxiliary. Committee members participated in the AMA Conference on the Impaired Health Professional, volunteered to work with the Board of Trustees Ad Hoc Committee on AIDS Policy, and recommended that APA take an active posture with state licensing boards regarding the importance of treatment and rehabilitation of psychiatrically impaired physicians without threat of license loss.

The *Committee of Residents,* Phyllis Amabile, M.D., chairperson, reported that several states require physicians applying for licensure or relicensure to list psychiatric treatment. This issue was discussed in detail at the beginning of this report. The committee made recommendations for improvements in the mechanism for nominations for Member-in-Training Trustee and Member-in-Training Trustee-Elect. The committee worked with the APA Committee on Member Life, Accident, and Health Insurance to prepare an article for publication in the newsletter of the American Association of Directors of Psychiatric Residency Training and the *Psychiatric Residents' Newsletter* on criteria for reimbursement of payments for psychotherapy and the implications such criteria would have for the future.

The *Committee on Independent Study,* Ian E. Alger, M.D., chairperson, continues to develop a catalog of independent study materials relevant to medical education. The committee has been evaluating a pilot study of independent case study material on a microcomputer floppy diskette. The demonstration of the interactive computer program for the case study has led the committee to consider a component workshop during the 1988 APA annual meeting on this educational technique. The committee explored the possibility of using the computer interaction for the Psychiatric Knowledge and Skills Self-Assessment Program (PKSAP) and the Psychiatry Resident In-Training Examination (PRITE).

The *APA/Burroughs Wellcome Fellowship Selection and Program Committee,* Walter E. Barton, M.D., chairperson, reported that 50 nominees were reviewed for the 1986–1988 program and 11 new fellows were selected. The committee asked that new guidelines for future evaluation of residents for the fellowship program be established, and the council agreed.

The *APA/Mead Johnson Fellowship Selection Committee,* James T. Barter, M.D., chairperson, reported that 15 new fellows and one alternate were selected. The committee is preparing an information form to provide a data base on candidate eligibility and noted that the selection criteria currently used should be updated.

The *APA Selection/Advisory Committee, APA/NIMH Minority Fellowship Program,* Charles A. Pinderhughes, M.D., chairperson, reported that 22 applicants were considered, eight fellows were selected, and three current fellows were selected as trainee-consultants. The committee asked, and the council recommended, that the joint Reference Committee consider adding an APA/NIMH Minority Fellow representative to the joint Reference Committee as an observer, that the program be allowed to seek outside funding to support the program if NIMH funding is not approved beyond the current budget period, and that the program be allowed to solicit donations for the newsletter, *SPECTRUM.*

The *Steering Committee, Psychiatric Knowledge and Skills Self-Assessment Program VI* (PKSAP-VI), Gordon D. Strauss, M.D., chairperson, reported on the completion of module B. The committee developed a schedule and a list of consultants for module C and moved toward the development of a method for the self-assessment of clinical skills. PKSAP-VI is divided into three modules; each module covers five topics, and one module per year will be distributed over 3 years. Distribution of the first section of module A began in the fall, and the other sections are being distributed at approximately 3-month intervals.

The *Task Force to Facilitate Communication Between the APA and the ABPN,* Richard I. Shader, M.D., chairperson, encouraged the development of review courses relevant to certification for Board candidates. The task force stated that the names of successful Board candidates will again be published in *Psychiatric News,* which will also include the names of those certified during the period when the names were not being published. The task force discussed subspecialization and recertification and expressed the opinion that there should be a sufficient, broad availability of programs for training in specific subspecialty areas and that these programs should provide adequate access to minorities, women, and foreign medical graduates. The task force reaffirmed its support for developing a critical incident examination that residents would be required to pass before graduation.

The *Committee on Psychiatrist Leadership in Public Mental Health Programs,* Steven E. Katz, M.D., chairperson, reported on its ongoing refinement of a paper on standards for state mental health directors. The committee completed the survey of state commissioners of mental health. The survey will be distributed to the National Association of State Mental Health Directors.

The *Task Force on Recertification,* Joe P. Tupin, M.D., chairperson, held its first meeting in several years during September. The task force planned various activities to inform the APA membership about the recent discussion on recertification and noted that the ABPN is planning to hold a workshop on recertification at the 1988 APA annual meeting.

The *Task Force on Cost Effectiveness in Consultation-Liaison Psychiatry,* Frederick Guggenheim, M.D., chairperson, presented the task force's final report at the council's retreat in July. The task force reviewed the existing literature on cost effectiveness in consultation-liaison psychiatry and compiled a bibliography on the subject. The bibliography is available from the APA Office of Education.

The *Task Force on* DSM-III-R *Educational Materials,* Michael Fauman, M.D., chairperson, held its first meeting in November. The task force is reviewing the need for and making recommendations concerning a wide range of educational activities to enhance members' knowledge about *DSM-III-R* and their ability to use the revised nomenclature. The task force also is developing model formats and materials to assist members in these endeavors.

The Council on National Affairs

Pedro Ruiz, M.D., Chairperson

During the past year, the council dealt with a series of important issues for both APA and the profession. In its work the council closely collaborated with the Assembly, the APA administration, and relevant APA components. In addition, the council provided leadership for its 13 components. Among the different key issues addressed by the council during this year, a few merit attention in this report.

The council organized the Corresponding Task Force on Victimization. The aim of this action was to develop effective clinical approaches to the special needs of victims of all the varied traumas in which victimization occurs. Along these lines, last winter the council held a special meeting with experts in national disasters to explore the need for a component in this area. In addition, the council sought and obtained the elevation of the Task Force on the Psychiatric Aspects of AIDS to committee status. This was done out of recognition of the impact of the acquired immune deficiency syndrome (AIDS) on all aspects of society and the need for APA to provide maximum expertise and leadership in the mental health issues related to this illness. Also, the council completed the organization of the Committee on Psychological Aspects of Nuclear Arms Development. Finally, the council also provided leadership and guidance in the formulation of policies and plans for its 13 components. A summary of these activities follows.

The *Committee on American Indian and Alaskan Native Psychiatrists,* Linda Cross, M.D., chairperson, was involved in the American Indian Physicians Association conference last summer in Spokane, Wash. The topics of this conference were violence and its impact on all aspects of the Indian community. This committee also visited the Indian Health Services in South Dakota during the summer. Special attention was paid during this visit to the problems created by alcoholism in the Indian population. Dr. Cross is also looking at the possibility of developing an Indian Mental Health Research Center at Michigan State University that would be geared toward the development of a model treatment program for the Indian population.

The *Committee on Asian-American Psychiatrists,* Joyce S. Kobayashi, M.D., chairperson, is exploring the development of a national data base on the health needs of Asian-American populations in the United States. This initiative was undertaken in collaboration with the Asian-American Health Forum. The committee is also identifying on a geographical basis the availability of Asian psychiatrists to assist monolingual Asian patients in the United States. This committee is looking at the possibility of creating an endowed lectureship for the APA annual meeting and is preparing a series of activities relating to specific Asian-American mental health needs for the next APA annual meeting.

The *Committee on Foreign Medical Graduates,* S. Arshad Husain, M.D., chairperson, continues to actively work with the American Medical Association to ensure appropriate input to the AMA on issues pertaining to foreign medical graduate physicians. The committee is actively working on the development of an international scholar program which would offer foreign medical graduate physicians an opportunity to receive training in the United States and later return to their countries of origin.

The *Committee on Gay, Lesbian, and Bisexual Issues,* James P. Krajeski, M.D., chairperson, is collaborating with the National Gay and Lesbian Task Force in combating violence against gay men and lesbians. This committee is actively developing an appropriate means to deal with the discrimination against gay men and lesbians that is present in some residency training programs and in psychiatric education. The committee is continuing its efforts to decrease all forms of discrimination against gay men and lesbians in the military.

The *Committee of Hispanic Psychiatrists,* Gladys Egri, M.D., chairperson, is investigating ways to provide adequate educational information regarding the different aspects of AIDS for the Hispanic population in the United States. This committee is also attempting to decrease the discriminatory practices currently employed by the U.S. Immigration and Naturalization Service regarding testing for the human immunodeficiency virus (HIV). The committee plans to publish a biographical directory of Hispanic psychiatrists. Finally, work on the Simon Bolivar Lecture to be presented at the 1988 APA annual meeting in Montreal next May has been completed by members of the committee.

The *Committee on Psychological Aspects of Nuclear Arms Development,* Judith Lipton, M.D., chairperson, had its first meeting during the last APA fall component meetings. This committee is organizing a series of presentations on nuclear issues for the next APA annual meeting in addition to attempting to establish appropriate liaison activities with professional organizations that have similar interests in this area. Finally, a series of publications on this theme will be prepared for *Psychiatric News, News for Women and Psychiatry,* and other key publications.

The *Committee on Occupational Psychiatry,* Duane Hagen, M.D., chairperson, has continued to provide consultation to employee assistance programs, particularly in areas related to stress. This component is also collaborating with the APA Joint Commission on Government Relations concerning employees' health insurance programs. The committee is organizing a workshop for the next APA annual meeting aimed at bringing focus and APA leadership to the subspecialty of occupational psychiatry.

The *Committee on Religion and Psychiatry,* Marc Galanter, M.D., chairperson, has finalized the details of the Oskar Pfister Award Lecture to be delivered by Dr. Oliver Sachs at the next APA annual meeting. Also, this committee finished the *Report on Cults and New Religious Movements,* soon to be published by American Psychiatric Press.

The *Committee on Women,* Nada L. Stotland, M.D., chairperson, is looking at ways to provide appropriate input in the planning of *DSM-IV.* The committee is also studying the need for an APA component on the psychiatric aspects of new reproductive technologies. Finally, this component is planning to hold a series of key activities pertaining to women's issues at the next APA annual meeting.

The *Committee on Psychiatric Aspects of AIDS,* Stuart E. Nichols, Jr., M.D., chairperson, is closely collaborating with APA's AIDS educational program and the Board of Trustees' Ad Hoc Committee on AIDS Policy and is continuing to provide leadership and education, particularly at the next APA annual meeting.

The *Committee on Abuse and Misuse of Psychiatry in the United States,* Roger D. Walker, M.D., chairperson, continued to focus on various areas in which psychiatrists and the profession are being discriminated against, such as detainment of children in psychiatric facilities without consent or psychiatric diagnosis and community mental health centers' misuse of psychiatrists. Further, the committee is planning a series of activities for the next APA annual meeting in which advocacy in these areas and others will be addressed.

The *Committee of Black Psychiatrists,* Thelissa A. Harris, M.D., chairperson, continued to develop appropriate links with national and federal entities geared toward the improvement and implementation of health and educational policies affecting black populations in the United States. Further, this committee focused on ways to minimize the impact of AIDS on black populations. Finally, this committee is in the process of organizing several activities for the next APA annual meeting focusing on homicide and violence in the black community.

The council worked hard to complete its agendas at the 1987 APA annual meeting and the 1987 APA fall component meetings and, for this, the council chairperson expresses his deepest appreciation to the council members: Lindbergh S. Sata, M.D. (vice-chairperson), David Kessler, M.D., Alexandra Symonds, M.D., Altha J. Stewart, M.D., Paul L. Adams, M.D. (consultant), Amado Suarez, M.D. (observer-consultant), Elissa P. Benedek, M.D. (Board liaison), Dorothy A. Starr, M.D. (Assembly liaison), Jonathan Sugar, M.D. (APA/Burroughs Wellcome Fellow), and Diane Felder, M.D. (APA/NIMH Fellow). Further, the council chairperson also thanks the members of all components under the council for their contributions. Finally, the council chairperson wishes to express his deepest appreciation to the APA staff, particularly Ms. Linda Roll, for providing invaluable assistance to the council during this year.

The Council on Psychiatric Services

Naomi Goldstein, M.D., Chairperson

This year, as in each year, the council and its components have been particularly concerned with access to psychiatric services in the public and private sectors for a broad range of populations and in all types of settings and have particularly emphasized the quality of care.

The council has many components and is still growing. At its fall meeting the council concluded that it must examine the effectiveness of its structure in responding to the needs of patients and members and to the concerns of APA components. Among its responsibilities, the council serves as a resource, as do all councils, for the joint Reference Committee and, through the joint Reference Committee, receives requests for opinions on a variety of issues from other components and, most important, the APA Assembly. Many significant issues were referred in 1987.

At the request of the joint Reference Committee and the Assembly, the council recommended that a conference be developed on psychiatry and health maintenance organizations. The steering committee has developed a tentative program, is seeking funds, and is developing a list of speakers for the conference, now identified as a resource symposium. The conference participants will be experts from both inside and outside APA, and it is anticipated that a sophisticated report will be developed and will subsequently be available to the membership and the district branches. It is hoped that this conference will be held in the fall of 1988.

In response to a referral, at its fall meeting the council recommended the development of a task force on clinician safety. Fortunately, violence toward clinicians is relatively rare, but when it happens it is unpleasant, occasionally fatal, and frequently preventable. The council consulted with the Joint Commission on Public Affairs and a representative of the National Alliance for the Mentally Ill and decided that the issue, although sensitive, must be actively addressed by APA.

The council also recommended the establishment of a task force on psychiatric services to mentally retarded and developmentally disabled adults, following a referral by the APA leadership and psychiatrists already working with this handicapped population. The emphasis of the task force would be on the provision of psychiatric services. The council understands that the lack of appropriate and adequate psychiatric services often makes management and provision of support services difficult and that there is a significant need to encourage psychiatrists to be involved in the care of these individuals.

Through the joint Reference Committee, the Assembly referred an action paper expressing its concern over access to services by minorities and underrepresented groups. The council studied this paper carefully. It recommended that the issue be referred to the Joint Commission on Government Relations and also back to the Assembly, which should encourage the district branches to establish their own procedures for studying the disparate services provided locally to various minority and underrepresented populations. A particular concern in the Assembly was the lack of psychiatric services to Indians. This issue was also addressed by the Council on National Affairs.

The Assembly also referred an action paper through the joint Reference Committee that was concerned with the development of guidelines for psychiatrists' signatures. For study purposes, the council began by discussing a recommendation on signatures from the Task Force on Professional Practice Issues in Organized/Managed Care Settings. The council is consulting with lawyers for APA and with the Committee on Ethics and later will be better able to develop a position. The issues involve psychiatrists signing medication prescriptions for patients they have not seen and, perhaps, signing insurance forms, treatment plans, or discharge orders without appropriate contacts. There are ethical, legal, and malpractice implications.

The council considered a statement referred to it on proposed standards for state mental health directors, which urged that only psychiatrists be selected to serve as state mental health directors. The council had some questions about this statement, which stirred up considerable discussion, and suggested that it be referred back to the Committee on Psychiatrist Leadership in Public Mental Health Programs for modification.

The council was privileged to have as its guest for dinner during the fall component meetings the incoming president of the National Alliance for the Mentally Ill, Mr. William Snavely. Mr. Snavely reviewed many issues on which various APA components could collaborate with the National Alliance for the Mentally Ill. That organization is not structured the same way as APA and does not necessarily have equivalent components. However, there are many issues on which medical leadership and joint expertise could be beneficial. It was felt that there could be enough agreement on issues to work toward defined positive results. The first step might be to narrow down the areas for collaboration and then to find individuals who could work together on those projects. It would seem that the increasing interest of the National Alliance for the Mentally Ill in the delivery of services and the problems experienced by patients and families is consistent with the frustrations and concerns of the council and its components, i.e., of psychiatry.

At its spring meeting, after a presentation by the Committee on Private Practice the council recommended to the joint Reference Committee that a component be developed to address problems in reimbursement and coding and, specifically, interpretation and use of the *Physician's Current Procedural Terminology (CPT)*. The Board of Trustees subsequently established the Work Group on Codes and Reimbursement, and members of the Committee on Private Practice and the council are actively involved in the work of this component.

The *Task Force on Professional Practice Issues in Organized/Managed Care Settings,* Haroutun Babigian, M.D., chairperson, was established in 1985 to address quality of care issues and to develop guidelines for psychiatrists working in community mental health centers (CMHCs), health maintenance organizations (HMOs), and other alternative delivery systems. The task force held workshops on HMOs and CMHCs at the annual meeting to gather opinions of psychiatrists on professional practice problems in both of these settings. The task force has already drafted guidelines for psychiatrists working in CMHCs, which were presented to the council. These have the support of the Committee on State Mental Health Systems and the Committee on the Chronically Mentally Ill, which recommended that these guidelines be shared with the National Council on Community Mental Health Centers and the American Association of Community Mental Health Psychiatrists for further discussion. The guidelines are under review by legal counsel, and it was suggested that they be compared with various standards of the Joint Commission on Accreditation of Healthcare Organizations (JCAHCO) to determine if there are any specific conflicts. The council hopes to present these guidelines to the joint Reference Committee this winter.

The *Committee on the Practice of Psychotherapy,* Marcia Goin, M.D., chairperson, has focused on educational issues and sponsored a program on the role of psychotherapy in the treatment of panic disorders at the 1987 annual meeting. The committee is developing a pamphlet titled "How Talking Helps," which it hopes will be used for patients but also in marketing efforts directed at employers. The committee is seeking examples of problems with reimbursement for psychotherapy and has met with the Committee on Financing and Marketing.

The *Task Force on Psychiatric Services in Jails and Prisons,* Henry Weinstein, M.D., chairperson, continues to work on a position statement and a set of guidelines for psychiatrists working in jails and prisons. The task force was informed that the conditions in several federal institutions are "inhumane" and that those conditions have serious negative psychological consequences. The task force is particularly concerned about this situation and noted an article in the *Nation* about psychological abuses of inmates. The task force sought guidance from the council, which advised it to seek further information and consult with other APA components.

The *Committee on Private Practice,* James A. Margolis, M.D., chairperson, submitted a number of articles to *Psychiatric News* that have been accepted for publication. It continues to present various educational programs at the annual meeting in conjunction with the Committee on Special Benefit Programs and expects to present a symposium at the 1988 annual meeting on private practice issues for residents. Each year the Committee on Private Practice sponsors a forum for private practice representatives of the district branches, and it hopes to expand this forum, to involve many more private practitioners, and especially, to encourage many more district branches to be represented. Not only is there a commonality of interests but some of the solutions might be applicable throughout the country.

The committee is particularly pleased with the establishment of the Work Group on Codes and Reimbursements. Two members of the committee have written a practical how-to article on the use of the *CPT*. The committee noted with some concern that the *CPT* is being used as a base for the Harvard Relative Value Scale Study, and it is hoped that APA can influence the direction of that study with respect to psychiatric codes.

The *Committee on Rehabilitation,* Arthur Meyerson, M.D., chairperson, reported that a number of APA members who are expert in psychiatric rehabilitation participated actively in work on the second edition of the American Medical Association's *Guide to Evaluation of Impairments*. In September 1987 the committee met with a representative of the AMA to consider yet another revision and was pleased to report that several members of the committee will be working actively with the AMA on reviewing the final draft.

The committee reviewed a grant proposal for a Social Security Administration research project that was submitted by APA. The committee expressed concern with the design and the procedure for submission, while noting the importance of the project. The committee recommended to the council that procedural guidelines be established for selecting appropriate areas of research and for ensuring appropriate component input. Dr. Meyerson agreed to draft such guidelines. APA was not awarded this grant, but submission procedures are under consideration by the Council on Research and by the APA leadership.

The *Committee on State Mental Health Systems,* Ernest Klatte, M.D., chairperson, sponsored a forum at the annual meeting that brought together various APA components with particular interest in state mental health systems. The committee hopes to publish a summary of the discussion at that meeting. It is also hoping to prepare a short version of this report to serve as a checklist of essentials for state officials and legislative bodies.

The committee has been working with the National Association of State Mental Health Program Directors, meeting with Mr. Harry Schnibbe, its director, and discussing Dr. Fuller Torrey's past survey and upcoming 1988 survey of state mental health systems. Of particular interest has been the relationship between state mental hospitals and CMHCs, which are considered interdependent but are usually organizationally isolated from each other. The committee would encourage efforts to bring together state commissioners of mental health, state hospital superintendents, and representatives of community programs to discuss their mutual concerns and to begin discussion of combining more of their efforts.

The committee is interested in having a permanent consultant from the National Alliance for the Mentally Ill and in working with the Council on Aging to discuss problems associated with mentally ill aged persons who are hospitalized because of behavioral disorders that cannot be dealt with in skilled nursing facilities. The committee reported that the Council on Aging is discussing the establishment of a task force to study these issues.

The *Committee on the Chronically Mentally Ill,* David Cutler, M.D., chairperson, has for the past year focused much of its energies on two issues, the homeless mentally ill and the training of professionals to work with the chronically mentally ill. Subcommittees have been organized to address the needs of the homeless mentally ill, chronically ill young adults, and patients with dual diagnoses, and an advisory group has been established for initiating curricula that focus on the chronically mentally ill. The committee reported that the National Institute of Mental Health (NIMH) and the Robert Wood Johnson Foundation have both sponsored nationwide initiatives to develop programs for the homeless and homeless mentally ill in cities throughout the country. The committee noted that there is relatively little literature on these issues and that these groups are still poorly defined, despite the large number of chronically mentally ill in the homeless population for whom homelessness itself is part of the course of the illness. The committee's workshops on the homeless at the 1987 and 1988 annual meetings and at the 1987 Institute on Hospital & Community Psychiatry have been considered priorities. Finally, members of the committee are working with other professionals involved in training people to work with the chronically mentally ill to put together a special issue of *Community Mental Health Journal* on training.

The *Committee on Drug Abuse,* Edward Kaufman, M.D., chairperson, prepared an update of APA's position on substance abuse in 1986, and it was published in the May 1987 issue of the *Journal.* The committee is now drafting an update of the 1969 APA position on the use of drugs of abuse in schools, working closely with the Council on Children, Adolescents, and Their Families.

The committee is concerned with the process of selection of reviewers and the absence of clinicians as reviewers for research proposals at the National Institute on Drug Abuse. The lack of funding for clinically oriented grants is under study by APA staff. The committee reported that the results of a recent survey of substance abuse fellowships in accredited psychiatry residency programs indicate there are 20 such fellowships and the number is increasing rapidly.

The *Committee on Alcoholism,* Richard Frances, M.D., chairperson, has been particularly concerned that the diagnosis-related groups (DRGs) for alcohol treatment will be implemented before an adequate impact analysis is done. It has consulted with the Division of Government Relations, which was somewhat pessimistic about the possibility of getting these DRGs changed but will continue to address their inappropriateness for alcoholism.

The committee has long emphasized the close relationship between alcoholism, drug abuse, and other psychiatric disorders and has been concerned that any reorganization involving NIMH and NIH might lead to a fragmentation of this relationship. The committee has been particularly in favor of formalizing a subspecialty on alcoholism, and possibly drug abuse, and suggested that an APA council on addiction be established to recognize the growth of this subspecialty. The committee has made several other suggestions to enhance collaboration between subspecialty groups and APA, and these will be explored further with other APA components.

The *Committee to Coordinate the Functions of the H&CP Service, Journal, and Institute,* H. Richard Lamb, M.D., chairperson, is responsible for overseeing the H&CP Service and for ascertaining that the Service, the *Hospital & Community Psychiatry* journal, and the Institute support each others' needs in terms of membership and participation. Efforts were made this year to collect all unpaid H&CP Service membership fees. Some members were dropped, but new members were enrolled, so the overall number of Service members remains about the same. The Service has developed and distributed several publications to subscribers, drawing on articles from *Hospital & Community Psychiatry.* Recent distributions have focused on chronically mentally ill young adults, the elderly mentally ill, and tardive dyskinesia. A new book on violence will be available in January 1988. The Service also hopes to add high-quality videotapes to its library. The Psychiatric Placement Service has been effective and has attracted new members to the H&CP Service, since a member of the H&CP Service is eligible for a discount on the placement fee. This in turn has increased the circulation of *Hospital & Community Psychiatry.* The recruiting service is growing and generates income for APA.

The *Committee on Federal Government Health Services,* William B. Hunter, M.D., chairperson, has been clarifying its mission and has been increasingly concerned with the low profile of public sector psychiatry. The committee reported that it had taken a quick poll of the council itself and found that a large number of its members either work part-time or have previously worked in the public sector. The population of those eligible to receive federal services is more than 30 million persons.

After a joint meeting with the Committee on Psychiatric Services in the Military, the Committee on Federal Government Health Services identified the following issues: professional identity issues in public psychiatry, recruitment and retention of psychiatrists, violent behavior, and the acquired immune deficiency syndrome (AIDS). The committee hopes to develop a network of psychiatrists in the public sector and, eventually, to recommend the establishment of a public psychiatry committee in each of the district branches.

The *Committee on Psychiatric Services in the Military,* Leonora Petty, M.D., chairperson, reported that within the last year a group of military psychiatrists had formed independently of APA. Of the 400 military psychiatrists contacted, 150 joined this new organization. One of their eventual goals is to become a "district branch" of APA. Military psychiatrists move frequently and find it difficult to become involved in local district branch activities and to obtain Fellowship status.

The committee has met with the APA Committee on Graduate Education, has had discussions with the Committee on Gay, Lesbian, and Bisexual Issues, and has been working with the Division of Government Relations. It is also consulting with the American Academy of Child and Adolescent Psychiatry on various CHAMPUS matters, including a proposed revision of CHAMPUS regulations that would permit mental health counselors to be authorized providers. The committee was concerned with the development of psychiatric inpatient DRGs in the Army, believing that, once established, these DRGs might be adapted to other services and, eventually, to other programs. The council encouraged the committee to work closely with the Division of Government Relations and to begin immediately.

The *Committee on Liaison With the American Hospital Association,* Mark A. Gould, M.D., chairperson, met twice with its counterpart from the American Hospital Association during the past year, and the agendas were extensive. The committee has recommended that the American Hospital Association and APA "collaborate in exploring the implications of AIDS in the areas of diagnosis, treatment, education, finance, delivery, and the law, with a view towards stimulating policy development by the appropriate components of both organizations." The council has forwarded this recommendation to the joint Reference Committee.

A second important issue has been managed care systems. Of concern are issues related to malpractice liability, educating consumers to be sure that there is adequate mental health coverage in these programs, and encouraging clinicians to object effectively when external utilization review decisions lead to inadequate treatment. Finally, the committee discussed extensively the inappropriate hospitalization of adolescents urging reasonable and sound response and leadership in this field.

The council also met with the Joint Commission on Public Affairs and the Joint Commission on Government Relations. Of particular interest was the meeting with the Council on Economic Affairs. The councils discussed the expected implementation of DRGs for alcohol and substance abuse treatment despite APA's opposition and also addressed the Health Care Financing Administration's continued interest in trying to use DRGs for psychiatry. The Council on Economic Affairs also reported on the Harvard Study on Relative Value Scales and various developments in the quality assurance field.

The councils jointly noted the special contribution made by Dr. Donald Hammersley to both councils and their many components over his many years as Deputy Medical Director. He brought wisdom, knowledge, and warmth to his role and provided a unique and highly sensitive presence to the work of the committees, particularly those with interests in the public sector and in the JCAHCO and quality assurance. His retirement from APA was noted with great regret and the best wishes of the council members.

The Council on Psychiatric Services met subsequently with Dr. Melvin Sabshin to share some of its concerns as Dr. Hammersley's many roles and responsibilities are reassigned.

Each year the chairperson must assure herself that the council is properly addressing its responsibilities on behalf of the membership and patients. She is grateful to the many components, individual psychiatrists, and staff persons who work with great dedication, energy, and expertise toward our mutual goals. She would like to recognize especially the extraordinary contribution of Ms. Corky Hart to the council's functioning.

The chairperson also wishes to thank vice-chairperson Bert Pepper, M.D.; council members J. Frank James, M.D., and Sheila Blume, M.D.; departing member Frank Rafferty, M.D., whose contribution to this council has been immeasurable; Rena Nora, M.D., observer-consultant; and Allison Doupe, M.D., APA/Burroughs Wellcome Fellow. The council is particularly indebted to Chester Schmidt, M.D., Board liaison, and to Gerald H. Flamm, M.D., and Seymour Gers, M.D., Assembly liaisons, who have been enormously effective in facilitating the work of this council.

The Council on Psychiatry and Law

Howard Zonana, M.D., Chairperson

The council continues to address major questions related to laws regulating psychiatric practices and to the use of psychiatric expertise in the resolution of legal issues. During the past year the council came to closure on a number of projects.

After review by the Assembly of District Branches, the Board of Trustees approved "The Physician's Duty to Take Precautions Against Patient Violence" as a resource document. This document presents a model legislative bill, which may be particularly useful in those states in which case law has expanded psychiatrists' liability beyond that established by the *Tarasoff* decision on the "duty to protect." Creating a resource document allows the Association to present guidelines to the membership without endorsing the "duty to protect" as official APA policy. During the past 2 years, approximately 10 states have passed legislation that limits the psychiatrist's duty to protect and defines the physician's responsibilities when a threat has been made regarding an identifiable victim. The approach outlined by the council would limit the causes of action against the psychiatrist in situations where the patient has communicated an explicit threat 1) to kill or seriously injure an identifiable victim or 2) to engage in destruction of property that is likely to lead to personal injury or death. The precautions taken by the physician would be considered adequate as a matter of law if the physician 1) communicates the threat to the identifiable victim, 2) notifies a law enforcement agency in the region, 3) arranges for the patient to be hospitalized, or 4) takes steps to initiate civil commitment. Immunity is provided for a psychiatrist who discloses confidential communications under these circumstances. This resource document was printed in APA's *State Update* to ensure the widest possible dissemination to the district branches. The council is also preparing an article that will present the background of this resource document and a more expanded discussion of the issues.

The council's proposed model regulation concerning the patient's right to refuse treatment is being reviewed by a representative group from the Assembly of District Branches. The model regulation includes two possible methods of addressing treatment refusal. In one view, if the patient was civilly committed, then the standard for review should be whether medication is necessary. Others feel that civil commitment and the patient's best interests are an insufficient standard for involuntary treatment and that specific competence to give or withhold informed consent to receive medication must be separately addressed. Both of these viewpoints are held by substantial numbers of practitioners and by scholarly reviewers of legal theory. The Assembly has appointed a task force that will review these issues and the council proposal.

The Board of Trustees approved for publication the report of the Task Force on Involuntary Outpatient Treatment. This report reviews both the theoretical foundation of the concept and the empirical literature and experience to date. Model statutory provisions are also presented, as well as problems experienced in several states that have passed such legislation. This report is intended to extend APA's guidelines for legislation on the psychiatric hospitalization of adults. The publication will be available in 1988.

The *Committee on Confidentiality,* Aaron S. Wolf, M.D., chairperson, has completed two projects. The Board of Trustees approved the committee's "Guidelines on Confidentiality." These guidelines were published in the November 1987 issue of the *Journal* and are also available in booklet form from American Psychiatric Press. This report emphasizes the importance of confidentiality and provides guidelines for ensuring confidentiality in a variety of practice settings. The committee has also drafted a model time-limited consent form for use by the psychiatrist when a patient requests disclosure of medical information. The time limit protects the patient by requiring requests for information to be made in a timely fashion and by requiring periodic review and consent by the patient. This form was reviewed by the Assembly of District Branches at the fall 1987 meeting. Committee members, with the assistance of APA's Division of Public Affairs, produced a videotape of vignettes regarding common problems with confidentiality and release of information. The videotape was shown at the committee's booth at the 1987 annual meeting, and a copy has been distributed to each Area for use as an educational tool. Another videotape will be prepared for use at the committee's booth at the 1988 annual meeting.

A subcommittee of the council is reaching closure on its review of the December 1982 APA position statement on the insanity defense. At the request of the Assembly, this subcommittee was formed to respond to specific questions. Several modifications of the original position paper will be recommended. For example, the 1982 position paper recommended that, when no realistic therapeutic justification for confinement exists, the insanity acquittee should be transferred from the hospital to a nontreatment facility that can provide the necessary security. Aside from the difficulty of assessing whether any further benefit from treatment can occur in the hospital, transfer to a correctional facility was not deemed either feasible or appropriate. In addition, the subcommittee has more fully developed some of the issues regarding testimony on the "ultimate issue," i.e., whether the defendant is "sane" or "insane," "responsible" or not, etc. The new federal guidelines do not permit such testimony, in accordance with the APA position paper. However, neither the position paper nor the courts have disallowed such opinions in psychiatric reports. The final report on the insanity defense position statement will be reviewed at the council's May 1988 meeting.

Dr. Zonana was appointed to serve on the Board's new Ad Hoc Committee on AIDS Policy. This committee requested that the council develop proposals regarding confidentiality and disclosure to third parties for patients with the acquired immune deficiency syndrome (AIDS). The council developed guidelines, which have been reviewed by the ad hoc committee and were approved by the Board at its December 1987 meeting. In developing these proposals, the council met with the Committee on Psychiatric Aspects of AIDS and the Committee on Confidentiality. Three proposals on the duty to warn were presented. In the first proposal, the Council stated that it is ethically permissible for the physician to notify any identifiable person the physician believes is in danger of contracting the AIDS virus from the patient if the patient 1) is infected with the human immunodeficiency virus (HIV) or has been diagnosed as having AIDS and 2) refuses to terminate behavior that places other people at risk or to notify identifiable individuals at risk.

In the second proposal, the council stated that it is ethically permissible for a physician to report to the appropriate public health agency the name of a patient who is determined by convincing clinical information about HIV infection or test records to be HIV positive if the physician has good reason to believe that the patient is engaging in behavior which places other persons at risk. The third proposal states that during an evaluation it is important for the physician to make clear the limits of confidentiality and, specifically, to notify the patient of the limits of confidentiality when inquiries about HIV status are made. The council also developed guidelines for confidentiality on inpatient psychiatric units. The guidelines describe considerations regarding disclosure of the patient's positive HIV test results to treatment staff and circumstances in which disclosure to other patients may be necessary. Additionally, members of the council will participate in a debate on this issue at the 1988 annual meeting.

The council began to examine the question of reporting mentally ill persons to state departments of motor vehicles. In Oregon, for example, state hospitals have been required to report each mentally ill patient who is unable to safely operate a motor vehicle at the time of discharge. It was the impression of some psychiatrists from that region that a few of these patients get their licenses back after discharge. There have also been some legal cases related to this issue, such as *Cain v. Rijken,* 717 P. 2d 140 (Or. 1986). The council is attempting to gather nationwide data on the medical reporting of impaired drivers and would appreciate hearing from members regarding their experiences in this area.

The issue of confidentiality in child custody determinations arose in the California case *Allred v. Superior Court.* The question there was whether a parent who brings a custody suit necessarily waives confidentiality regarding past psychiatric treatment merely by raising the question of fitness to parent. In some jurisdictions, under the doctrine of the best interest of the child, judges will frequently rule that the privilege is waived and allow for disclosure of such records. In other jurisdictions, when the privilege is not deemed waived, an expert called in to evaluate the current capacity of the parent may feel handicapped in performing an adequate evaluation without access to prior records. There is clearly a need to control inappropriate requests or "fishing expeditions" yet, at the same time, allow a complete evaluation when it is relevant. Because of the complicated issues raised by this case, the council proposed and the Board approved establishment of a task force to consider this issue in full.

The council has also proposed the establishment of a task force to examine the use and misuse of psychiatric diagnoses in the courts. Seymour Halleck, M.D., in a series of published and working papers, has begun to explore some of these difficult issues. As stated in the initial *DSM-III* caveat, "It is to be understood that inclusion here, for clinical and research purposes, of a diagnostic category such as Pathological Gambling or Pedophilia does not imply that the condition meets legal or other nonmedical criteria for what constitutes mental disease, mental disorder or mental disability." This has not been a sufficient deterrent to misuse of psychiatric diagnostic criteria. This task force, approved by the Board in December 1987, will examine the relevancy of psychiatric diagnoses to forensic evaluations and legal determinations, discuss the limits of psychiatric diagnoses, and attempt to clarify the tasks involved in forensic evaluations. This work would also be important in the development of *DSM-IV.*

During the past year, other council-related activities included Dr. Loren Roth's participation in a work group convened by the joint Reference Committee to prepare an APA response to the United Nations Commission on Human Rights document "Principles, Guidelines and Guarantees for the Protection of Persons Detained on Grounds of Mental Ill-Health or Suffering from a Mental Disorder" (the Daes report). The work group extensively rewrote the report, and APA has submitted this revision and a critique of the U.N. draft report to the United Nations. In addition, Dr. Zonana chaired a committee that prepared a report for the Helsinki Commission on Guidelines for the Examination of Potential Defectors. The committee was established by the Helsinki Commission and includes council members referred by APA.

The Council on Research

Herbert Pardes, M.D., Chairperson

The Council on Research has begun to function under its new structure and organization, which were reported to the APA membership in the *Journal* a year ago. Two of the proposed committees, the Committee on Psychiatric Diagnosis and Assessment and the Committee on Research on Psychiatric Treatments, have been formally established and they have held their first meetings. (Summaries of the activities of these two committees and other components of the council follow.) The Committee on Science Policy will be initiated later during the year. In the meantime, the council continues to review and track science policy issues and activities.

During the past year the Council on Research monitored a number of important developments in psychiatric research. These included the searches for a new administrator of the Alcohol, Drug Abuse, and Mental Health Administration and a new director of the National Institute of Mental Health (NIMH), federal budget/appropriations issues, mental health research at the Veterans' Administration, the reorganization and placement of NIMH, animal research issues, and the initiation of research grants and awards made by other groups, such as the American Mental Health Fund and the National Alliance for Research on Schizophrenia and Depression.

The council met with leaders of the National Institute of Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and NIMH to review research and research training priorities and developments within these organizations.

The council, in concert with the Scientific Program Committee and others, sponsored several successful sessions at the 1987 annual meeting in Chicago. These included New Research Session 1—"Science Policy: The Future of Psychiatric Research and Research Training" and "Research Advances in Psychiatry: An Update for the Clinician." Plans for participation in the 1988 annual meeting are being formulated.

The council has been overseeing the APA Social Security Disability Evaluation Study, which has completed its data collection. Preliminary study findings were presented to the Task Force on Social Security Income/Social Security Disability Insurance and the Committee on Rehabilitation during the 1987 fall component meetings. Because of the extended focus on data collection, additional time was needed to complete the data analysis and prepare the report, and the Social Security Administration extended funding for the project and changed the deadline to Nov. 11, 1987. (The initial deadline for completion of the project was September 10.) The council applauded Drs. Cille Kennedy and Samuel Simmens for their excellent work and extended its thanks for a superb job.

The council is canvassing several organizations to determine their guidelines on the ethical implications of two funding issues. The first is pharmaceutical companies' payment of psychiatrists to participate in clinical trials of psychotropic agents. The second issue concerns fee-for-service research, whereby psychiatrists are paid by the patients in research studies. The council plans to pursue these topics further at its spring 1988 meeting.

The council is in the process of obtaining funding for a task force on prevention research to examine this emerging field, summarize the existing information, and identify prevention research opportunities.

Currently the council has 11 components. Highlights of their activities follow.

The *Committee on the Biographical Directory and Related Research,* David Knesper, M.D., chairperson, has distributed a biographical survey to APA members who joined the Association after 1982. This survey is intended to be used partially as a test of the survey instrument for the upcoming survey of the entire membership. The committee hopes that the questionnaire will list a member's previously published biographical information so that the member will need only to update this information. The committee anticipates that the full member survey will be distributed in late 1987 or early 1988 and hopes that the next *Biographical Directory* will be available by summer or fall 1988.

The committee has received proposals for seven piggyback surveys for the all-member survey. These will be reviewed by the Council on Research, and those approved will be distributed with the all-member survey.

The *Committee on Psychiatric Diagnosis and Assessment,* Allen Frances, M.D., chairperson, held its first meeting in September 1987. The committee spent a considerable amount of time discussing the development of future classification systems for mental disorders, focusing on the need for proceeding in a timely fashion, the process for development and approval, and the concerns expressed both by internal and external groups. The report emanating from the committee's first meeting reflected a thoughtful and detailed consideration of the pros and cons of a number of procedural and process questions related to future classifications, and these were subsequently circulated to the Area councils, Assembly, and Board of Trustees to facilitate a dialogue on the issues.

The *Committee on Research on Psychiatric Treatments,* John Kane, M.D., chairperson, also held its first meeting in September 1987. This committee will oversee the treatment-related components currently under the aegis of the Council on Research and explore technology assessment issues and treatment issues generally, including options for follow-up to the activities of the Task Force on the Treatments of Psychiatric Disorders.

The *Task Force on Benzodiazepine Dependency,* Carl Salzman, M.D., chairperson, is drafting a report on dependence on and withdrawal from benzodiazepines. The task force will meet during the American College of Neuropsychopharmacology annual meeting to review and finalize the second draft of this report. Dr. Salzman believes the work of this task force will be extremely useful to the average practitioner. The task force also has been charged with a second task—to look at both the abuse potential and behavioral toxicity of benzodiazepines. Work on this part of the report is just being initiated.

The *Task Force on Sudden Death,* George Simpson, M.D., chairperson, presented its final report, "Sudden Death in Psychiatric Patients: The Role of Neuroleptic Drugs," to the council in September. The council reviewed the document and agreed that it is useful, comprehensive, and thoughtful. The report was also reviewed by Joel Klein, APA legal counsel, and he did not believe it has liability implications. The council recommended to the Board of Trustees that the report be published as an APA monograph in the task force report series.

The *Task Force on Development of Safety and Performance Standards for ECT Devices,* Richard Weiner, M.D., chairperson, reported that the APA petition to reclassify ECT devices from class III to class II, first submitted in 1983, is still pending. The task force anticipates that the U.S. Food and Drug Administration (FDA) will agree to the reclassification for the clinical indication of depression but not for mania or schizophrenia. When the proposed regulation comes out, APA will have an opportunity to present documentation supporting the inclusion of mania and schizophrenia before the final regulations are approved. The task force will also encourage a number of other organizations to write to the FDA in support of APA's position.

The task force is now beginning to focus on its new charge (approved by the Board of Trustees in June 1987), which includes the development of general guidelines for the practice of ECT, a basic core of knowledge and skills expected of ECT practitioners, recommendations for training and education, suggestions for the implementation of these guidelines, and other recommendations. Permission was given to the task force to seek outside funding in support of the new charge, and negotiations with NIMH have been initiated. To accommodate the new charge the task force requested that its membership be expanded and that its name be changed. The Council agreed to recommend to the joint Reference Committee and the Board of Trustees that, in view of the expanded charge, the name of the current task force be changed to simply the Task Force on Electroconvulsive Therapy.

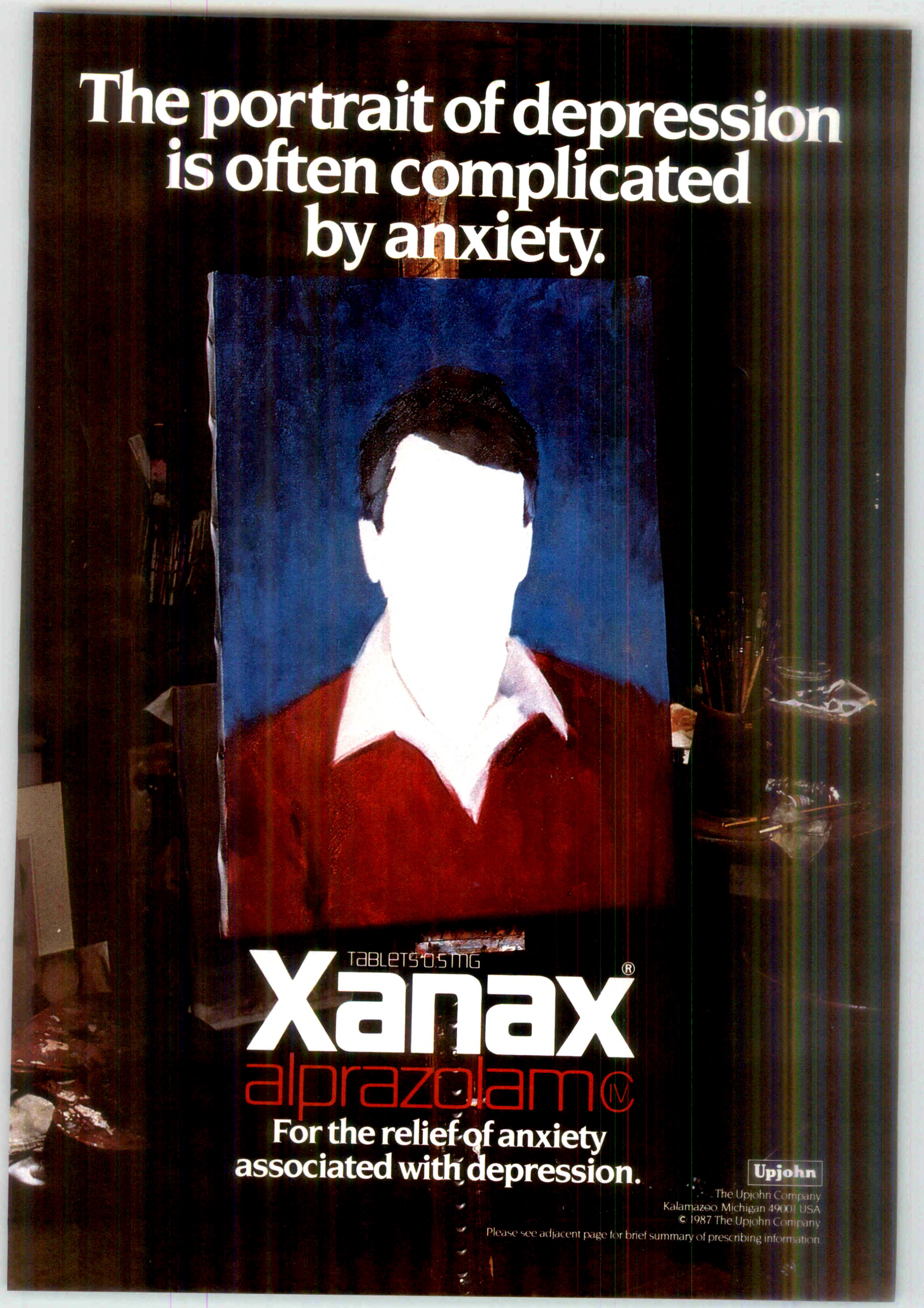
The *Task Force on Tardive Dyskinesia,* John Kane, M.D., chairperson, is finalizing a report on tardive dyskinesia. In addition, the task force recently sent letters to a number of pharmaceutical companies to solicit support for the production of several educational films on tardive dyskinesia. It intends to target the films to several audiences: psychiatrists, nonpsychiatric physicians, and patients and their families.

The *Task Force on Treatments of Psychiatric Disorders,* T. Byram Karasu, M.D., chairperson, announced that the work of the task force is almost complete and that all chapters of the report have been distributed for comment to consultants and others who requested them. The Board of Trustees approved a number of recommendations from the ad hoc committee of the Board and Assembly appointed to review the report of this task force, including the recommendations that 1) the report of the Task Force on Treatments of Psychiatric Disorders be published by APA as a task force report with the disclaimers approved earlier (to follow), 2) the title of the publication be "Treatments of Psychiatric Disorders," 3) the schedule be based on the best efforts of the chairperson and American Psychiatric Press to complete the editing and indexing in an acceptable fashion, 4) Dr. Karasu's name appear prominently on the publication, and 5) the book appear in three volumes and individual monographs be extracted from the total work and sold separately if there appears to be a demand for them. (The disclaimers approved by the Assembly and Board of Trustees earlier in the year read, "This report does not represent the official policy of the American Psychiatric Association. It is an APA task force report, signifying that members of the APA have contributed to its development, but it has not passed through those official channels required to make it an APA policy document. This report is not intended to be construed as, or to serve as, a standard for psychiatric care.")

The *Task Force on Psychosocial Treatment Research,* John Docherty, M.D., chairperson, is examining the current state of psychosocial treatment research and the role of psychiatrists in that research. The task force is currently reviewing journal articles, identifying sources and extent of funding, and developing a survey of those currently engaged in psychosocial treatment research. Its objectives will be to communicate to psychiatrists major advances that have occurred through psychosocial treatment research, develop methods to facilitate the funding of such research across all disciplines, determine the reasons for diminished psychiatric participation in such research, develop and propose mechanisms for facilitating increased research on psychosocial treatment by psychiatrists, and develop a position statement on the current role of psychosocial treatment and research competence in psychiatry with a proposal for a model curriculum for residency and continuing education training.

The *Task Force on the Use of Laboratory Tests in Psychiatry,* Alexander Glassman, M.D., chairperson, realized publication of its report on the dexamethasone suppression test, which appeared in the October 1987 issue of the *American Journal of Psychiatry.* The status of the task force is now under review to determine if there are other tasks to be completed or if the task force should be disbanded.

The report of the *Task Force on the Long-Term Effects of Lithium on the Kidney,* George Heninger, M.D., chairperson, is still pending.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Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

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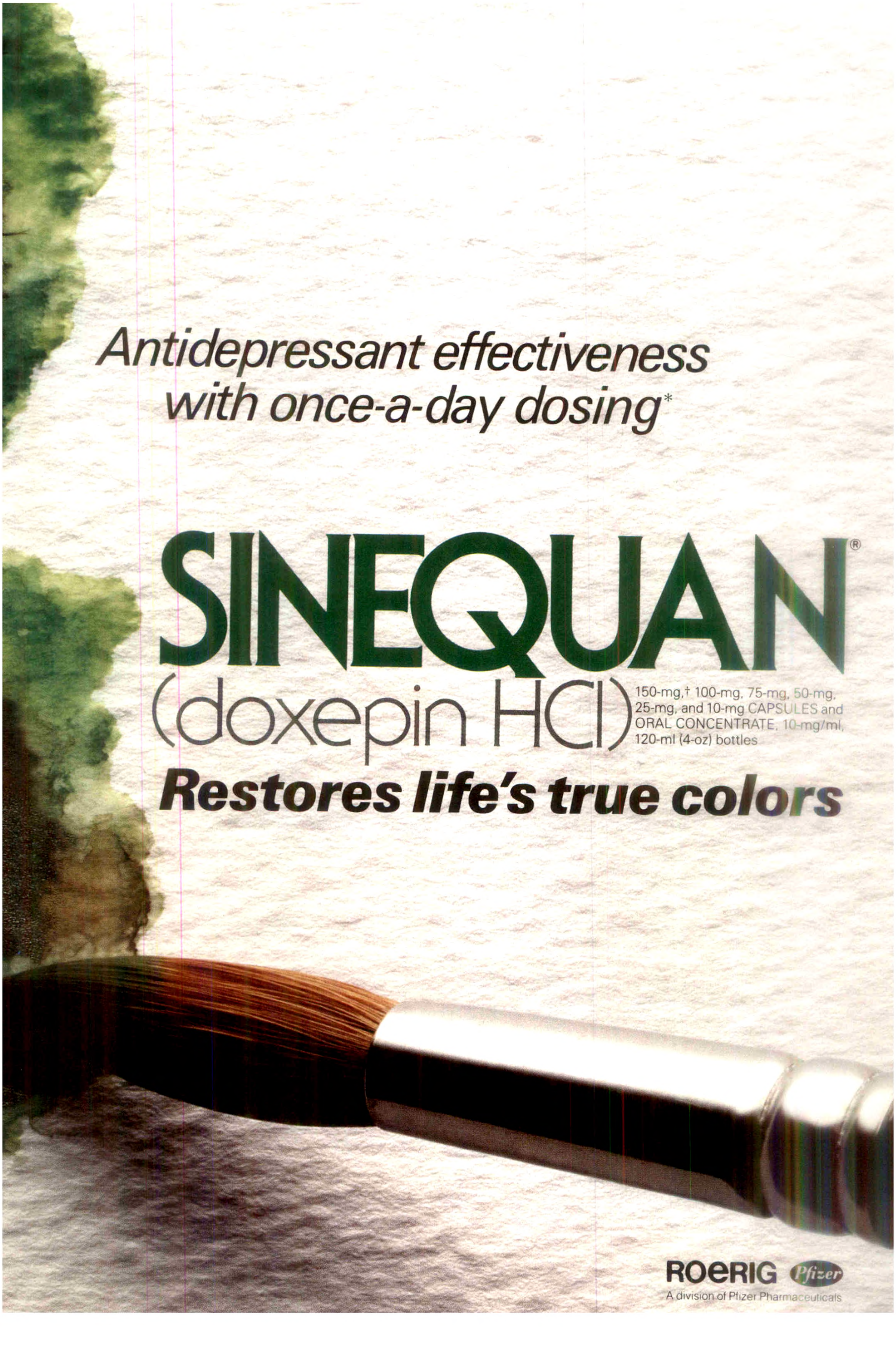

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Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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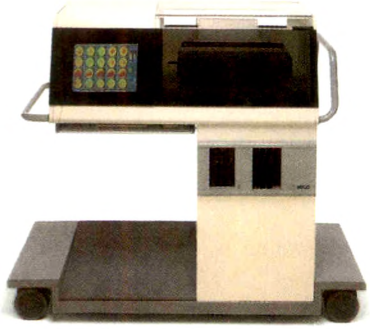

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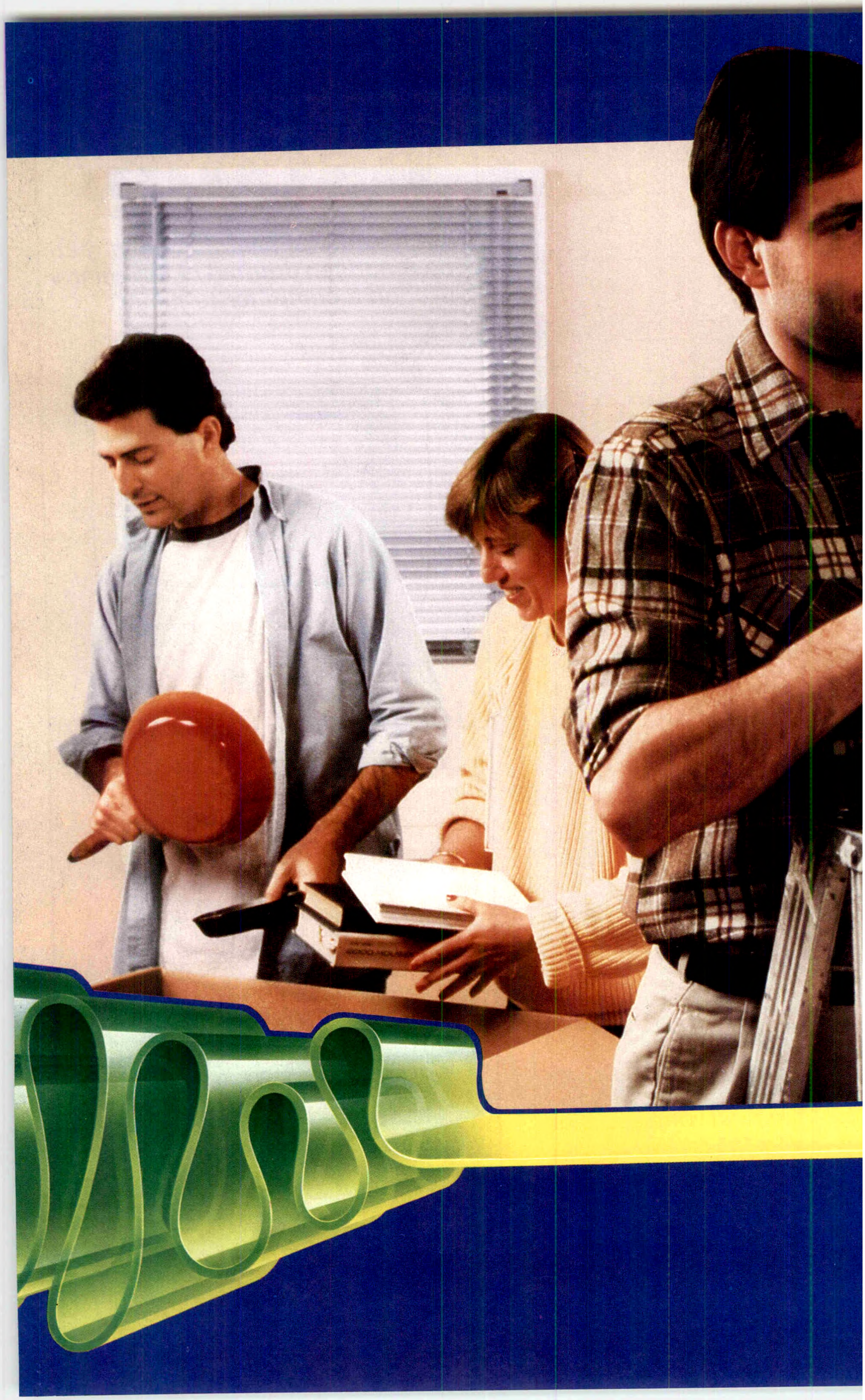


For the schizophrenic patient

Sustained protection from relapse

About 60% of schizophrenic patients will experience relapse at some time.[1] Because of the increased risk of deterioration with each relapse, today's therapeutic challenge is to use all available measures to prevent its occurrence.[2] The sustained drug delivery of once-monthly HALDOL Decanoate Injection can be one factor in reducing the risk of relapse. Monthly administration assures that patients receive the prescribed dose of medication.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

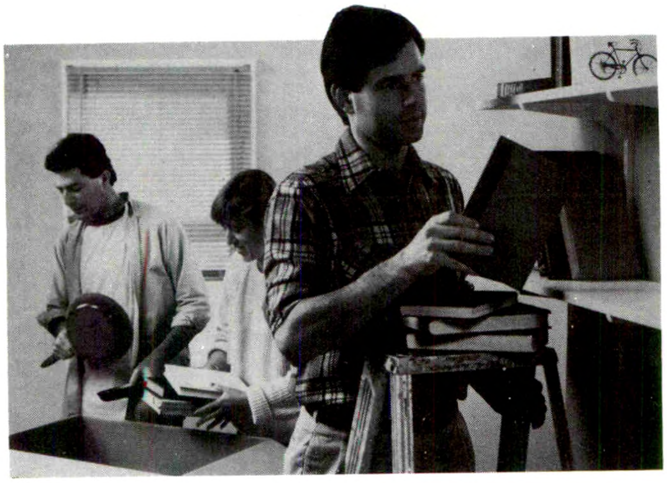
References:
1. Johnson DA: Epidemiological evaluation of maintenance antipsychotic treatment, in Tognoni G, Bellantuono C, Laher H (eds): *Epidemiological Impact of Psychotropic Drugs.* Amsterdam, Elsevier/North Holland Biomedical Press, 1981, pp 205-220.
2. Lehmann HE, Cancro R: Schizophrenia: clinical features, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry,* ed 4. Baltimore, Williams & Wilkins, 1985, vol 1, pp 680-713.

Please see brief summary of Prescribing Information on next page.

Once-monthly

HALDOL® DECANOATE

(HALOPERIDOL) INJECTION



HALDOL® DECANOATE

(HALOPERIDOL) INJECTION

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired live function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes i impossible to determine definitively what role, if any, HALDOL played in the outcome of th reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, bu it is to be kept in mind that sudden and unexpected death may occur in psychotic patients whe they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate i administered or prescribed.
For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychoti patients with moderately severe to very severe symptoms.

6/3/8

For additional information, please call:
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The appointment is subject to final budgetary approval. Applications, including a curriculum vitae and names of three referees, should be sent to Dr. James E. Miles, Head, Department of Psychiatry, The University of British Columbia, 2211 Wesbrook Mall, Vancouver, B.C., Canada, V6T 2B5.

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada.

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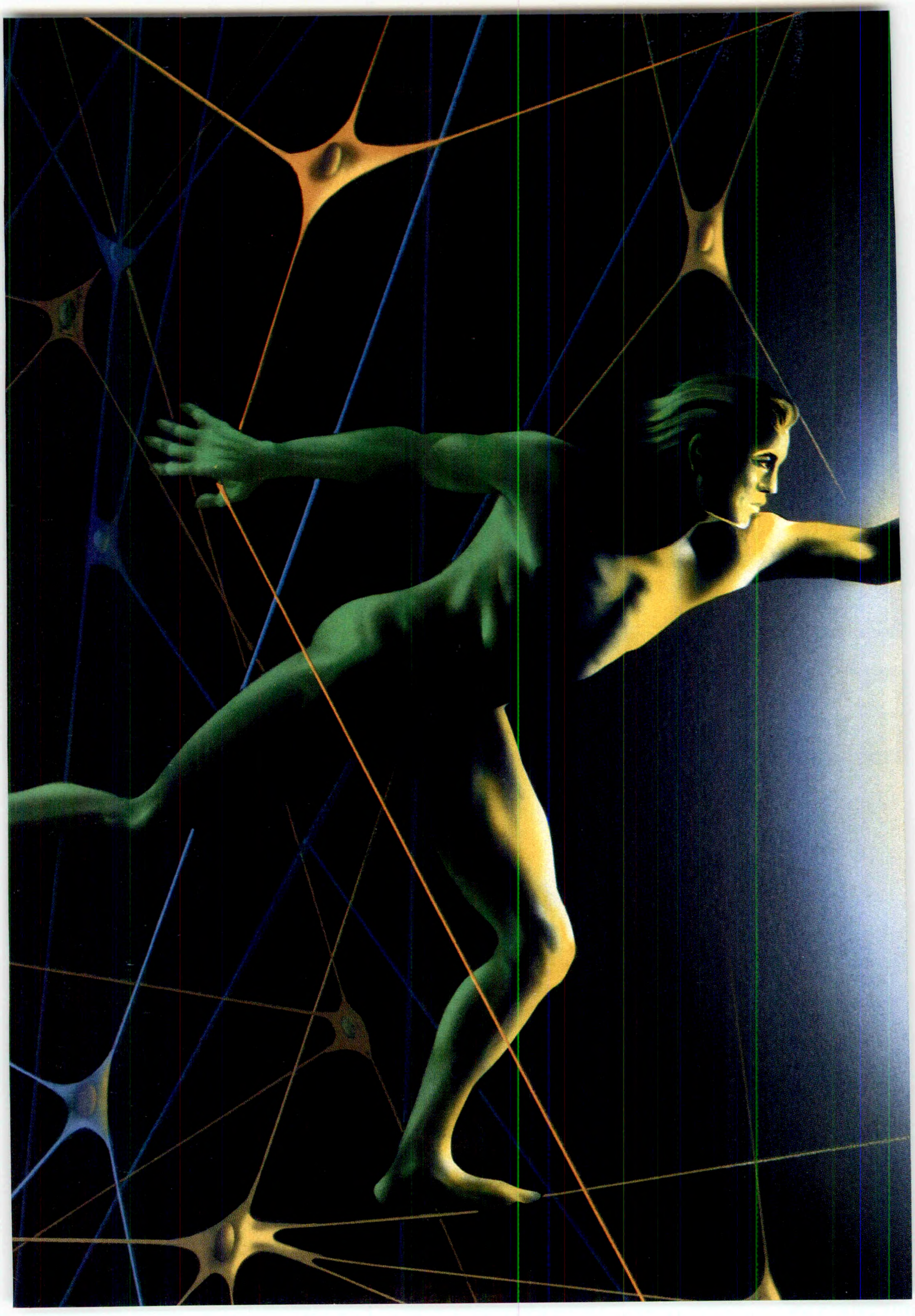
Responses, including C.V., should be sent to:

Alan J. Wabrek, M.D.
Chairman, Search Committee
Hartford Hospital
80 Seymour Street
Hartford, CT 06115



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Fewer side effects than anticholinergics may encourage compliance with neuroleptic therapy

☐ Unlike anticholinergics, SYMMETREL is not associated with memory impairment[2]

☐ Fewer atropine-like side effects than anticholinergics for greater patient comfort

☐ Available in capsules and a raspberry-flavored syrup

Please see following page for brief summary of prescribing information.
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATION: Drug-induced Extrapyramidal Reactions: SYMMETREL (amantadine hydrochloride) is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with the anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The adverse reactions reported most frequently (5 – 10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1 – 5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1 – 1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

Bottles of 100	NDC 0056-0105-70
Bottles of 500	NDC 0056-0105-85
Hospital Unit-Dose Blister Package of 100	NDC 0056-0105-75

As a syrup (each 5 ml [1 teaspoonful] contains 50 mg amantadine hydrochloride) in:

16 oz. (480 ml) bottles	NDC 0056-0205-16

Store at controlled room temperature (59° – 86°F, 15° – 30°C).

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702 and Banner Gelatin Products Corp., Chatsworth, California 91311, for Du Pont Pharmaceuticals.

References:
1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: amantadine versus benztropine. *World J Psychosynthesis* (special issue) 1984-1985; 16:40-43. **2.** McEvoy JP, McCue M, Spring B, et al: Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry* 1987; 144(5):573-577.

* D.F. Casey, *N. Engl. J. Med.* 298:516. 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 4 April 1988

In this issue:

The Right to Refuse Treatment With Antipsychotic Medications: Retrospect and Prospect
By Paul S. Appelbaum

Empathy: Misconceptions and Misuses in Psychotherapy
By Howard E. Book

Adverse Cutaneous Reactions to Antidepressants
By Julia K. Warnock and John W. Knesevich

Official Journal of the American Psychiatric Association

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Ativan® doesn’t
significantly delay clearance because of age or kidney or liver dysfunction

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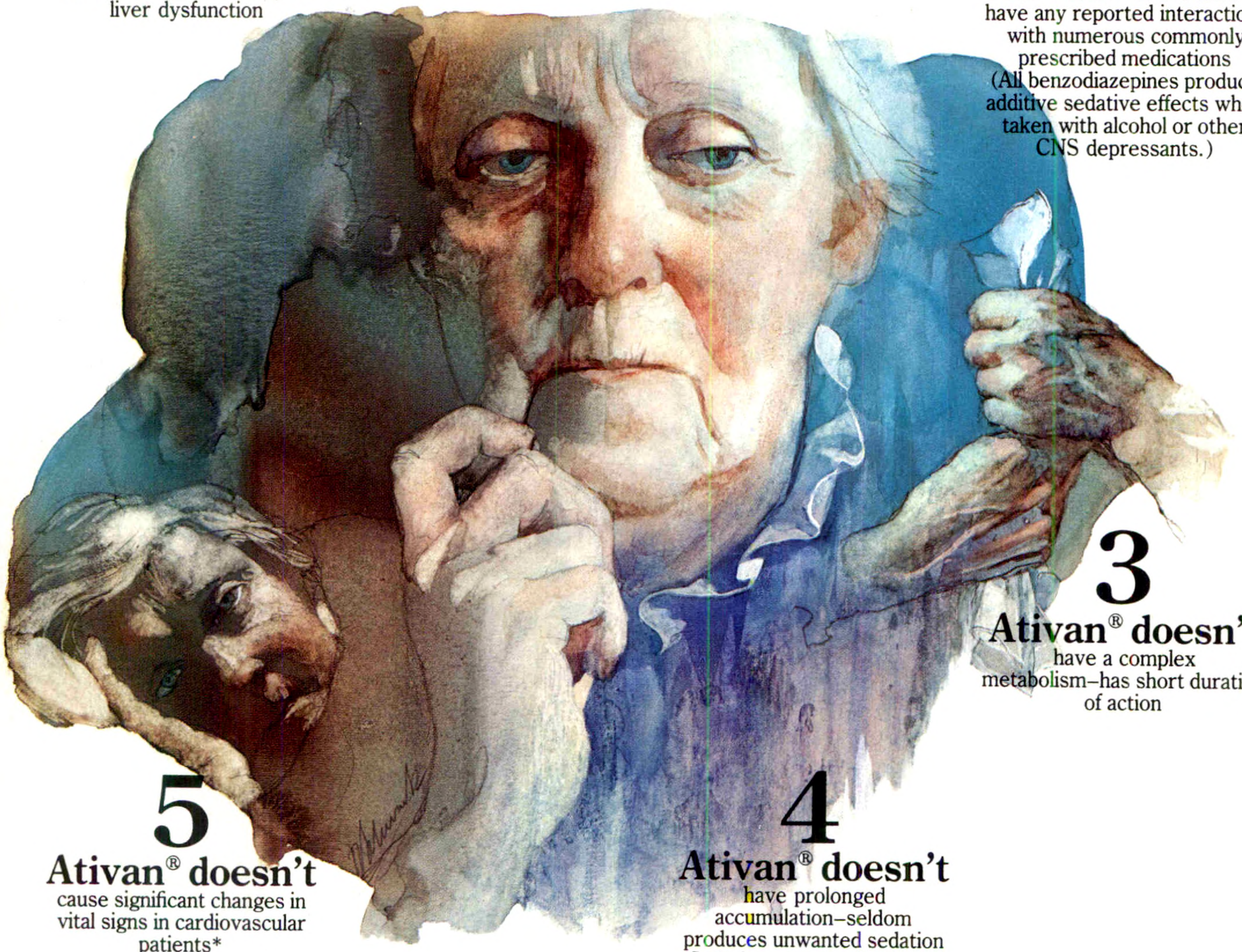
Ativan® doesn’
have any reported interactio
with numerous commonly prescribed medications
(All benzodiazepines produce
additive sedative effects whe
taken with alcohol or other CNS depressants.)



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have a complex
metabolism–has short duratio
of action

4

Ativan® doesn’t
have prolonged accumulation–seldom produces unwanted sedation (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

5

Ativan® doesn’t
cause significant changes in vital signs in cardiovascular patients*

…it does effectively relieve anxiety

Ativan®
(lorazepam) Ⓒ IV

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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rapid relief of anxiety

clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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Indicate one of the following on your prescriptions, as appropriate to your state laws:

- ■ Do not substitute
- ■ Dispense as written
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- ■ Brand necessary
- ■ May not substitute
- ■ No substitution
- ■ NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

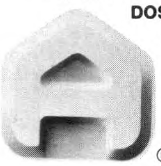
PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.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DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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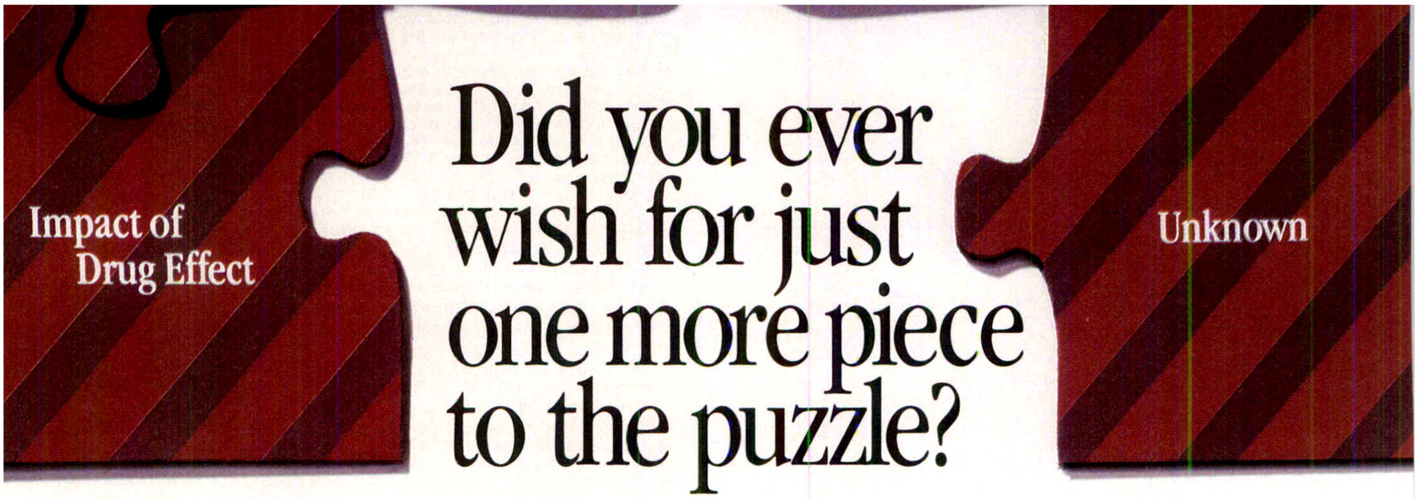

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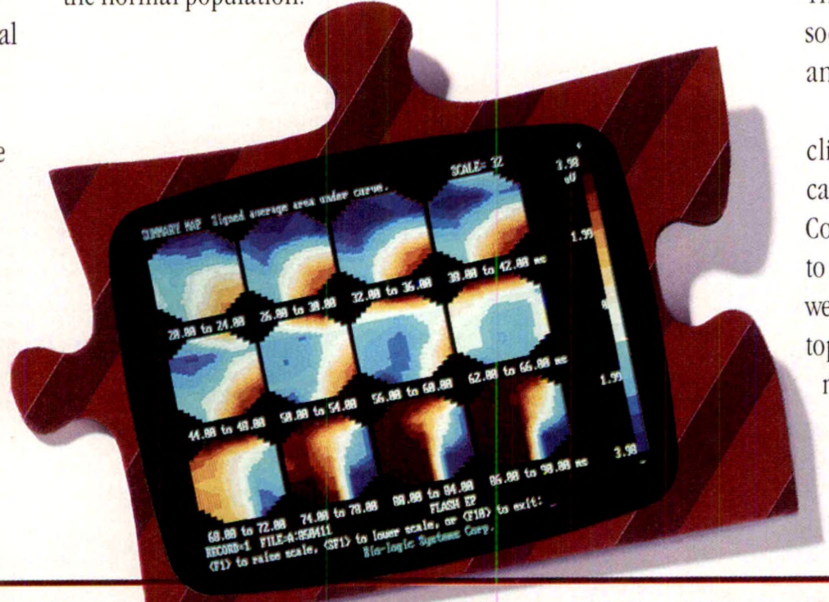

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SUMMARY MAP  Signed average area under curve.           SCALE= 32
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68.00 to 72.00  74.00 to 78.00  80.00 to 84.00  86.00 to 90.00 ms
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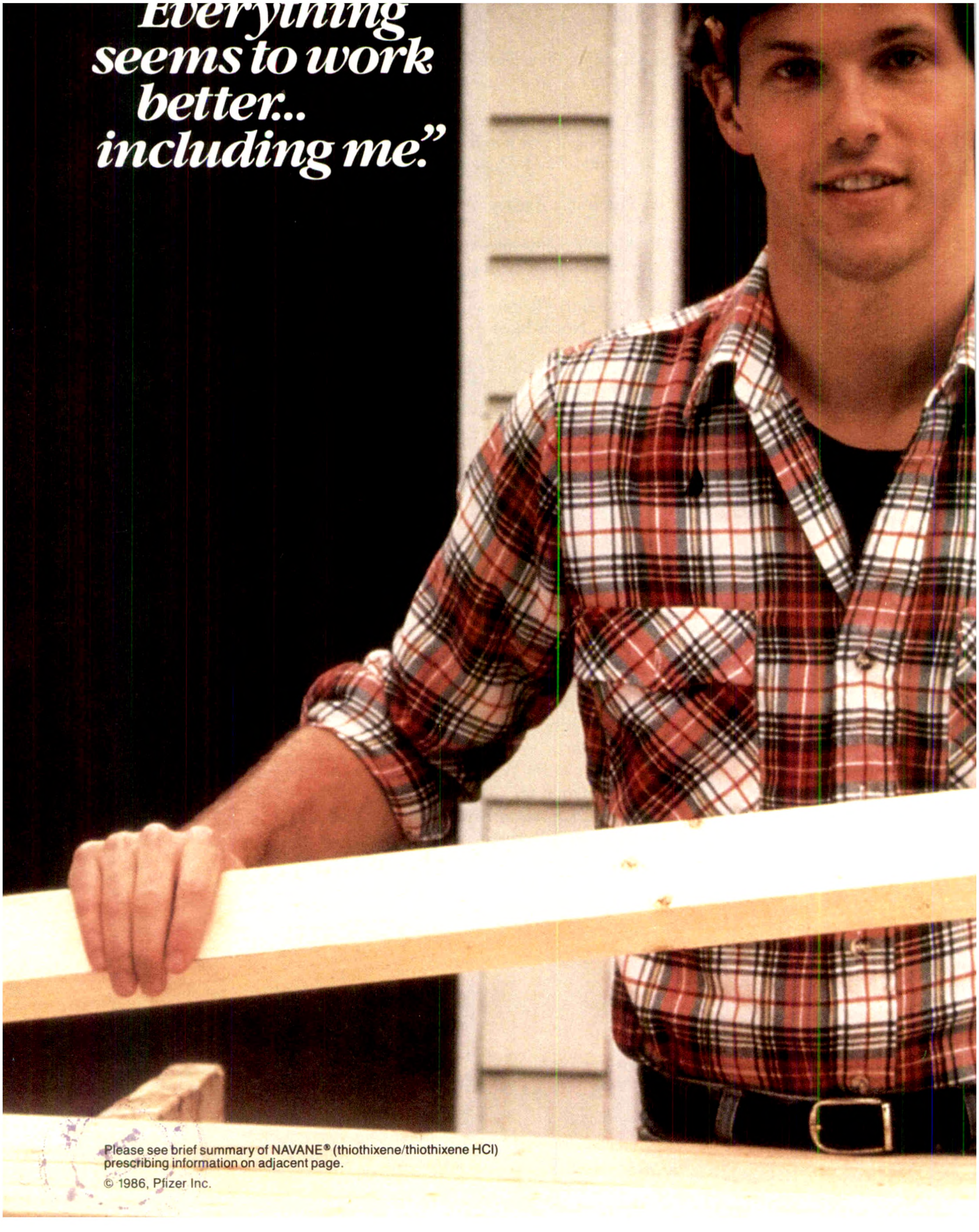
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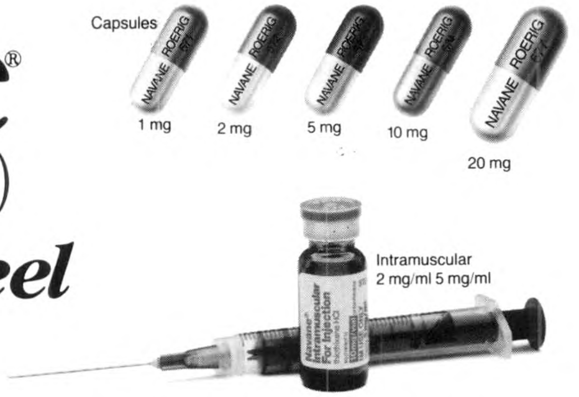

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
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Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged
periods). Blood dyscrasias (agranulocytosis, pancytopenia, thromboc
(jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reac
on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparatio
injected well within the body of a relatively large muscle. The preferre
of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in c
then only with caution to avoid radial nerve injury. Intramuscular inje
lower and mid-thirds of the upper arm. As with all intramuscular inject
avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists du
culture experiments indicate that approximately one third of human bre
in vitro, a factor of potential importance if the prescription of these dr
a previously detected breast cancer. Although disturbances such as
mastia, and impotence have been reported, the clinical significance
unknown for most patients. An increase in mammary neoplasms has
administration of neuroleptic drugs. Neither clinical studies nor epide
however, have shown an association between chronic administration
igenesis; the available evidence is considered too limited to be conclus

Information for Patients—Given the likelihood that some patients ex
develop tardive dyskinesia, it is advised that all patients in whom chro
possible, full information about this risk. The decision to inform patie
viously take into account the clinical circumstances and the compete
information provided.

Adverse Reactions: *Note:* Not all of the following adverse reaction
(thiothixene). However, since Navane has certain chemical and pharm
azines, all of the known side effects and toxicity associated with phen
mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness
sion occurs, epinephrine should not be used as a pressor agent since a
pressure may result. Nonspecific EKG changes have been observed
(thiothixene). These changes are usually reversible and frequently dis
The incidence of these changes is lower than that observed with some
cance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it us
Navane therapy. The incidence of sedation appears similar to that of the
but less than that of certain aliphatic phenothiazines. Restlessness, agi
with Navane. Seizures and paradoxical exacerbation of psychotic sy
infrequently.

Hyperreflexia has been reported in infants delivered from mothers
drugs.

In addition, phenothiazine derivatives have been associated with ce
abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisi
Management of these extrapyramidal symptoms depends upon the ty
symptoms may require the use of an injectable antiparkinson agent. M
be managed by reducing the dosage of Navane and/or administering

Persistent Tardive Dyskinesia: As with all antipsychotic agents tar
patients on long-term therapy or may occur after drug therapy has
characterized by rhythmical involuntary movements of the tongue, fa
tongue, puffing of cheeks, puckering of mouth, chewing movements
panied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients sh
sis. It has been reported that fine vermicular movement of the tongue
If this or any other presentation of the syndrome is observed, the clini
tinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline p
been infrequently observed in some patients. No clinically confirm
Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic
which are usually transient, can occur occasionally with Navane. Oth
sociated with agranulocytosis, eosinophilia, hemolytic anemia, thron

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and
reported with Navane. Undue exposure to sunlight should be avoi
Navane, exfoliative dermatitis and contact dermatitis (in nursing perso
phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and
percentage of females receiving Navane. If persistent, this may nec
discontinuation of therapy. Phenothiazines have been associated wit
necomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion,
creased salivation, and impotence have occurred infrequently with
been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiti
weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is
therapy and the occurrence of a systemic lupus erythematosus-like s

Neuroleptic Malignant Syndrome (NMS): Please refer to the te
section.

NOTE: Sudden deaths have occasionally been reported in patients
azine derivatives. In some cases the cause of death was apparently c
of the cough reflex. In others, the cause could not be determined nor
due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted dependin
condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatme
information.

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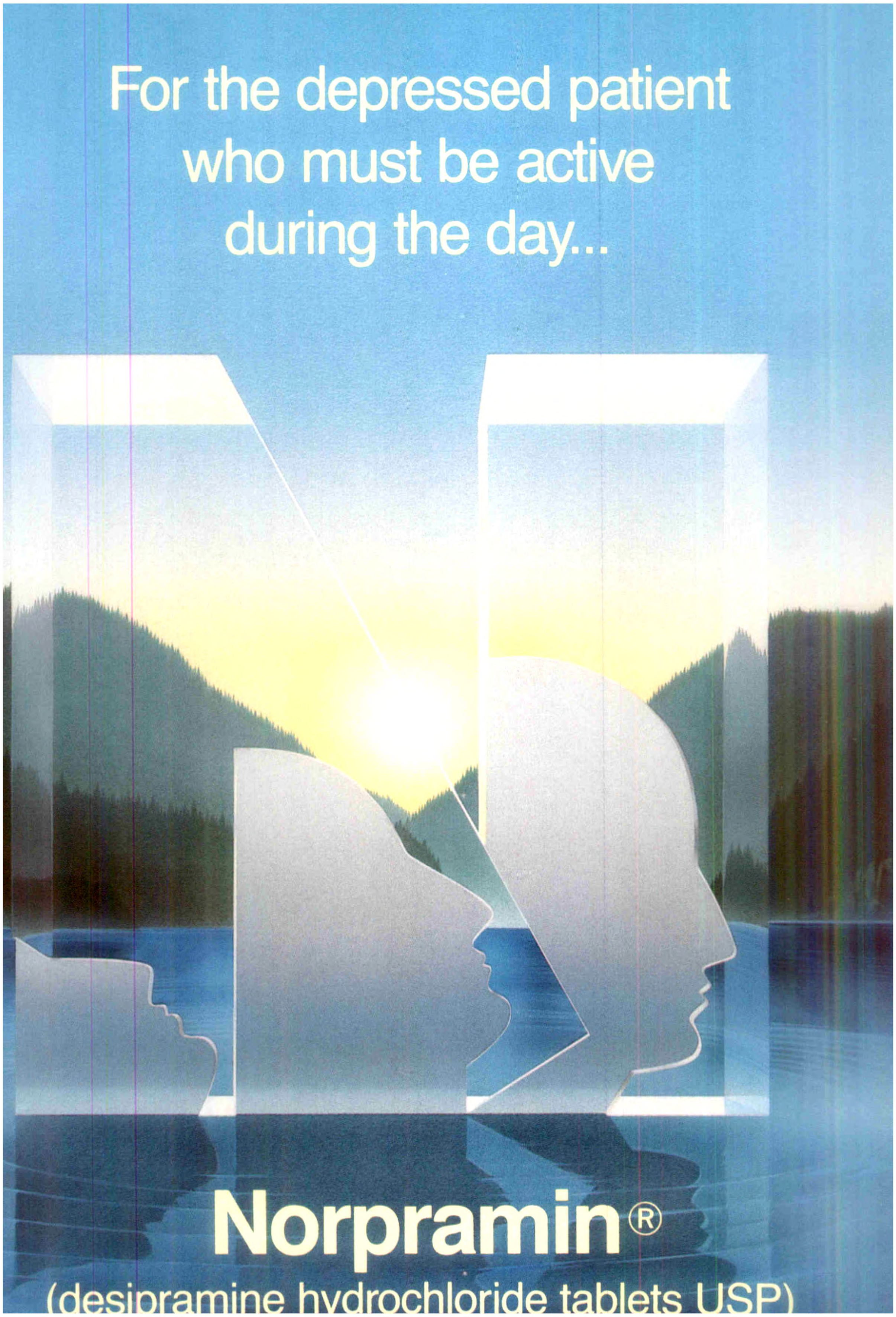

For the depressed patient
who must be active
during the day...

Norpramin®

(desipramine hydrochloride tablets USP)

Norpramin® 10, 25, 50, 75, 100, 150 mg

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a logical choice among antidepressants

Now after 23 years

- Norpramin is the #1 prescribed antidepressant by psychiatrists for the 2nd year in succession (based on a national prescription audit through July, 1987)

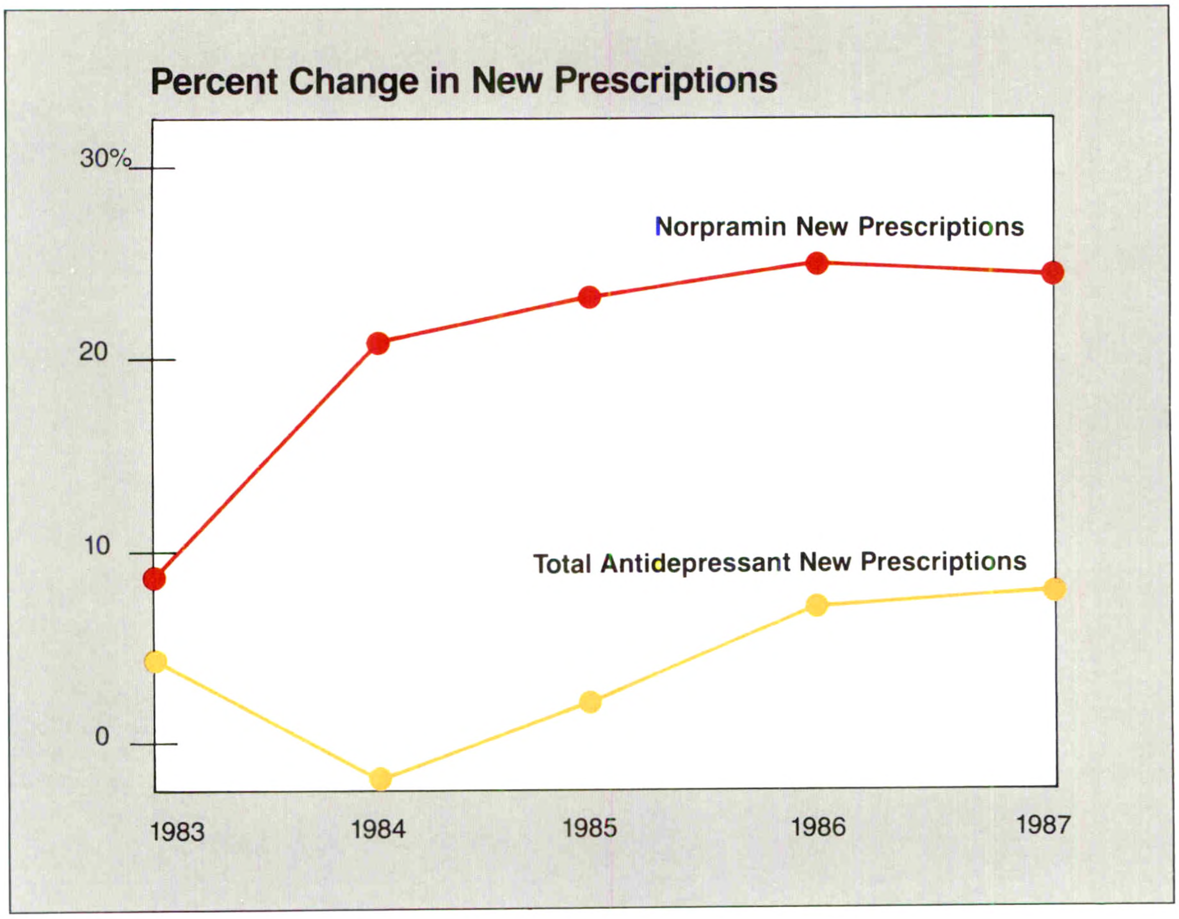

Figure 1. The red line tracks the percent change in new Norpramin prescriptions. The yellow line represents the total new prescription activity for the antidepressant market (based on data from a national prescription audit through July 1987).

Merrell Dow

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

a logical choice among antidepressants

The reasons are clear

- A 23-year record of efficacy in relieving symptoms of depression, including somatic anxiety,[1] sleep disturbances[2]
- Less anticholinergic activity than amitriptyline or doxepin, as shown in studies in the laboratory[3] and in normal human subjects[4,5] (see Warnings)
- Usually no excessive daytime drowsiness* (see Warnings)
- A well-defined clinical profile
- Unexcelled dosage flexibility, for patient convenience and compliance, for cost savings to patient...

*Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

References:

1. Nelson JC, Mazure C, Quinlan DM, and Jatlow PI: Drug responsive symptoms in melancholia. Arch Gen Psychiat 1984; 41:663-668.
2. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45215.
3. Snyder SH and Yamamura HI: Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiat 1977; 34:236-239.
4. Blackwell B, Stefopoulos A, Enders P, Kuzma R and Adolphe A: Anticholinergic activity of the tricyclic antidepressants. Am J Psychiat 1978; 135:722-724.
5. Petersen GR, Blackwell B, Hostetter RM, Kuzma R and Adolphe A: Anticholinergic activity of the tricyclic antidepressants despiramine [sic] and doxepin in nondepressed volunteers. Communic Psychopharmacol 1978; 2:145-150.

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See Prescribing Information on the next page

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

Convenient choice of 6 tablet strengths and once daily or divided dosage allows titration to individual response

10 mg 25 mg 50 mg 75 mg 100 mg 150 m

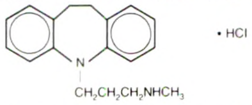
Norpramin®

(desipramine hydrochloride tablets USP)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Norpramin (desipramine hydrochloride USP) is an antidepressant drug of the tricyclic type, and is chemically: 5*H*-Dibenz [*b*,*f*] azepine-5-propanamine, 10, 11-dihydro-*N*-methyl-, monohydrochloride



INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: ACAcia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**

   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**

   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, *Metabolism*). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less clo correlated with plasma levels.Clinical symptoms of intolerance, especially drowsiness, dizziness, postural hypotension, should also alert the physician to the need for reduction in dosage. Pla desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and complianc

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical respons a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and complianc

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypoten shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of imp conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precep early evacuation of the ingested material and subsequent support of respiration (airway and movem circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, ca pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospital tion and close observation are generally advisable, even when the amount ingested is thought to be s or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormal should have continuous cardiac monitoring for at least 72 hours and be closely observed until well cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most o anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repe at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be g Because of the short duration of action of physostigmine, the effective dose should be repeated at minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possi of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dial Because of indications that the drug is secreted in gastric juice, constant gastric lavage has suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopr agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice fo control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhyda which has less central depressant effect but also has an effect on heart rhythm that has not yet been defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and o are probably the initiating events in shock. Intravascular volume must be maintained by i.v. f Digitalization should be carried out early in view of the fact that a positive inotropic effect ca achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

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  NDC 0068-0011-61: unit dose dispenser of 100
  NDC 0068-0011-10: bottles of 1000
50 mg green coated tablets imprinted MERRELL 15 or NORPRAMIN 50
  NDC 0068-0015-01: bottles of 100
  NDC 0068-0015-61: unit dose dispenser of 100
  NDC 0068-0015-10: bottles of 1000
75 mg orange coated tablets imprinted MERRELL 19 or NORPRAMIN 75
  NDC 0068-0019-01: bottles of 100
100 mg peach coated tablets imprinted MERRELL 20 or NORPRAMIN 100
  NDC 0068-0020-01: bottles of 100
150 mg white coated tablets imprinted MERRELL 21 or NORPRAMIN 150
  NDC 0068-0021-50: bottles of 50

Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect excessive heat.

Product Information as of April, 1987 Y

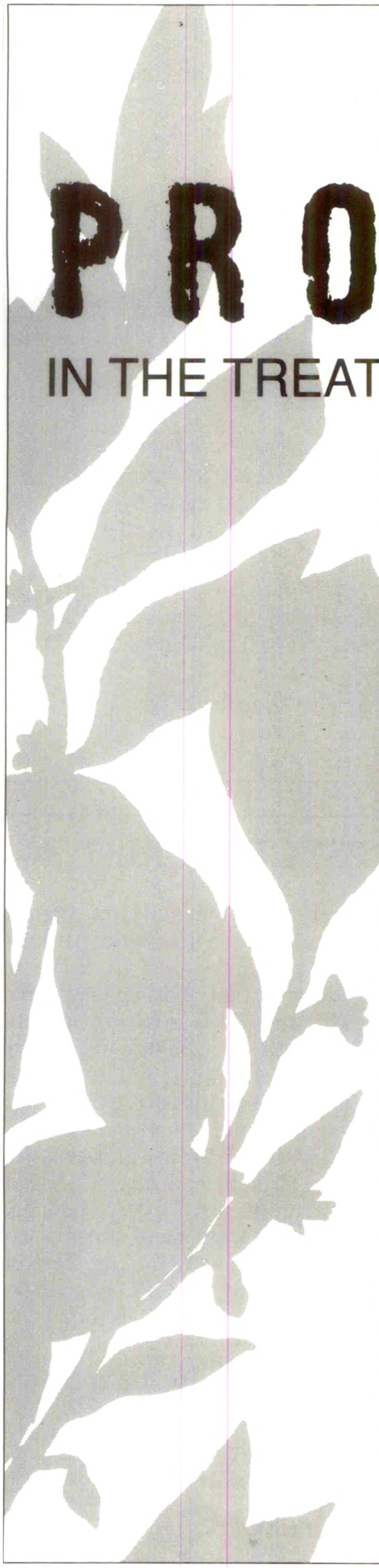
MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

8-0110(NR047) MDA037

November, 1987

Printed in U.S



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PROGRESS

IN THE TREATMENT OF COCAINE ABUSE

Chairman:
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Tuesday evening,
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Program- 7:00pm-10:00pm

This special symposium will examine progress in treating cocaine addiction by reviewing data from significant controlled trials using antidepressants and other pharmacologic agents, and will also discuss promising nonpharmacologic therapies and relapse prevention strategies. The program will explore the biobehavioral and biochemical bases for addiction and will also cover the medical complications of cocaine use.

PROGRAM AND FACULTY

Introduction
Herbert D. Kleber, MD
Professor of Psychiatry,
Yale University
New Haven, Connecticut

Overview of Pharmacologic Interventions for Cocaine Abuse
Frank H. Gawin, MD
Assistant Professor of Psychiatry,
Yale University
New Haven, Connecticut

Evaluation and Clinical Management of Cocaine Abusers
Robert B. Millman, MD
Professor of Psychiatry,
Cornell University Medical College,
New York, New York

Cocaine: PET Findings
Lewis R. Baxter, Jr., MD
Assistant Professor of Psychiatry and Biobehavioral Sciences
University of California, Los Angeles,
Los Angeles, California

Medical Toxicity of Cocaine
Jeffrey M. Isner, MD
Associate Professor of Medicine and Pathology
Tufts University School of Medicine
Boston, Massachusetts

DISCUSSANTS

Marian W. Fischman, PhD
Associate Professor
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Charles O'Brien, MD
Vice-Chairman,
Department of Psychiatry
University of Pennsylvania
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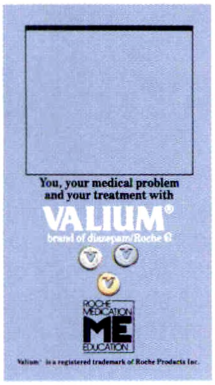
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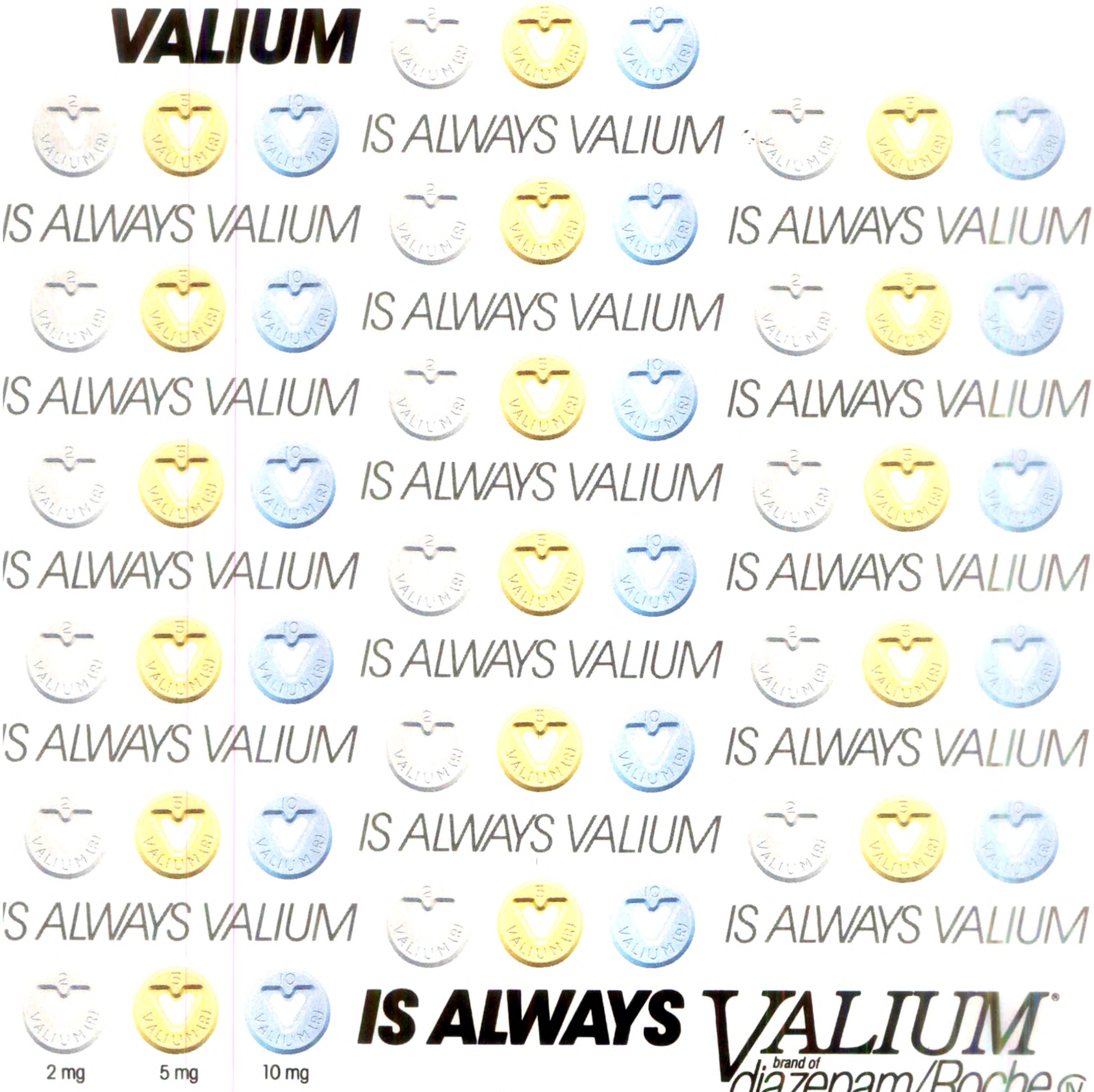

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Books Received

From Social Class to Social Stress: New Developments in Psychiatric Epidemiology, edited by Matthias C. Angermeyer. New York, Springer-Verlag, 1987, 310 pp., $77.60.

Treating Chronically Mentally Ill Women, edited by Leona L. Bachrach, Ph.D., and Carol C. Nadelson, M.D. Washington, D.C., American Psychiatric Press, 1988, 184 pp., $19.95.

Homicide, by Martin Daly and Margo Wilson. New York, Aldine DeGruyter, 1988, 321 pp., $42.95; $18.95 (paper).

Behaviour Problems in Mental Handicap: An Annotated Bibliography 1970–1985, by Kenneth Day, Joyce Hamilton, and Paul Smith. London, Gaskell, 1988, 111 pp., £7.50 (paper).

Counseling Individuals: The Rational-Emotive Approach, by Windy Dryden, Ph.D. Philadelphia, Taylor & Francis, 1987, 197 pp., $24.00 (paper).

Ethics and Psychiatry: Toward Professional Definition, by Allen R. Dyer, M.D., Ph.D. Washington, D.C., American Psychiatric Press, 1988, 168 pp., $32.00.

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The Psychiatry of Handicapped Children and Adolescents: Managing Emotional and Behavioral Problems, by Joan P. Gerring, M.D., and Lucille Parkinson McCarthy, Ph.D. Boston, College-Hill (Little, Brown and Co.), 1988, 246 pp., $24.50 (paper).

Profile Analysis: Auditory Intensity Discrimination, by David M. Green. New York, Oxford University Press, 1988, 136 pp., $35.00.

Preventing Teenage Suicide: The Living Alternative Handbook, by Polly Joan. New York, Human Sciences Press, 1986, 149 pp., $24.95; $12.95 (paper).

To Love and to Work: A Demonstration and Discussion of Psychotherapy (1976), by Leonard H. Kapelovitz, M.D. Northvale, N.J., Jason Aronson, 1987, 246 pp., $25.00.

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Perceiving Similarity and Comprehending Metaphor: Society for Research in Child Development Monograph 214, by Lawrence E. Marks, Robin J. Hammeal, and Marc H. Bornstein. Chicago, University of Chicago Press, 1987, 100 pp., $9.75 (paper).

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An Annotated Bibliography of DSM-III, edited by Andrew E. Skodol, M.D., and Robert L. Spitzer, M.D. Washington, D.C., American Psychiatric Press, 1987, 574 pp., $38.50.

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Principles of Medical Psychiatry, edited by Alan Stoudemire, M.D., and Barry S. Fogel, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich) (Philadelphia, W.B. Saunders Co., distributor), 1987, 692 pp., $79.00.

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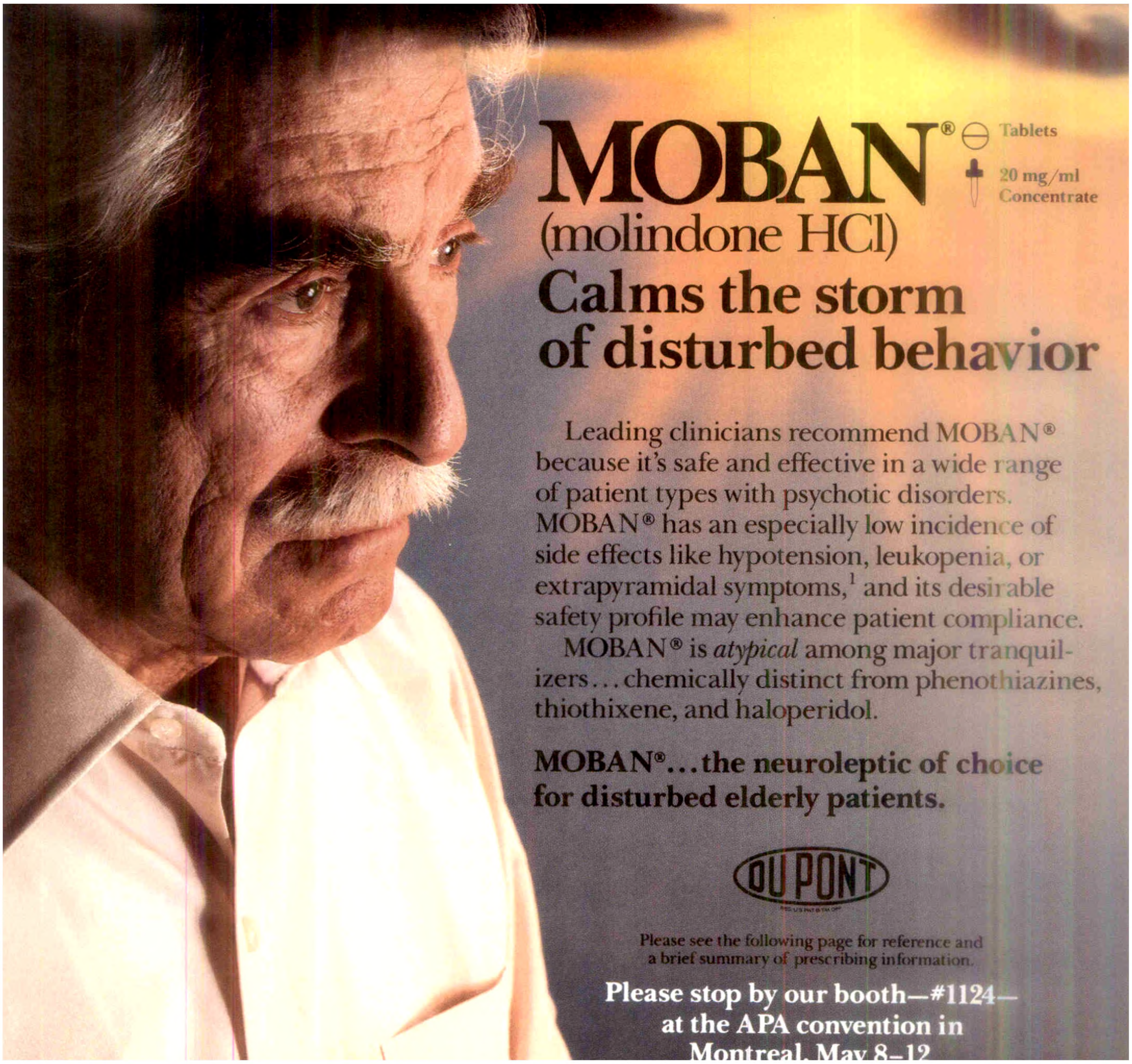
Invisible Trauma: The Psychosocial Effects of Invisible Environmental Contaminants, by Henry M. Vyner, M.D. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1988, 213 pp., $29.00.



MOBAN® (molindone HCl)

Tablets

20 mg/ml Concentrate

Calms the storm of disturbed behavior

Leading clinicians recommend MOBAN® because it's safe and effective in a wide range of patient types with psychotic disorders. MOBAN® has an especially low incidence of side effects like hypotension, leukopenia, or extrapyramidal symptoms,[1] and its desirable safety profile may enhance patient compliance.

MOBAN® is *atypical* among major tranquilizers . . . chemically distinct from phenothiazines, thiothixene, and haloperidol.

MOBAN®. . . the neuroleptic of choice for disturbed elderly patients.

DU PONT

Please see the following page for reference and a brief summary of prescribing information.

Please stop by our booth—#1124— at the APA convention in Montreal, May 8–12

MOBAN® (molindone hydrochloride)

Brief Summary of Prescribing Information

INDICATIONS: MOBAN is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of MOBAN was established in clinical studies which enrolled newly hospitalized and chronically hospitalized, acutely ill, schizophrenic patients as subjects.

CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause, and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may suppress or partially suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic suppression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS Effects: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms. One patient being treated with MOBAN experienced priapism which required surgical intervention, apparently resulting in residual impairment of erectile function.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

Concentrate: 20 mg/ml in 4 oz (120 ml) bottles.

Reference: 1. Peper M: Clinical experience with molindone hydrochloride in geriatric patients. *J Clin Psychiatry* 1985; 46 (sec 2): 26-29.

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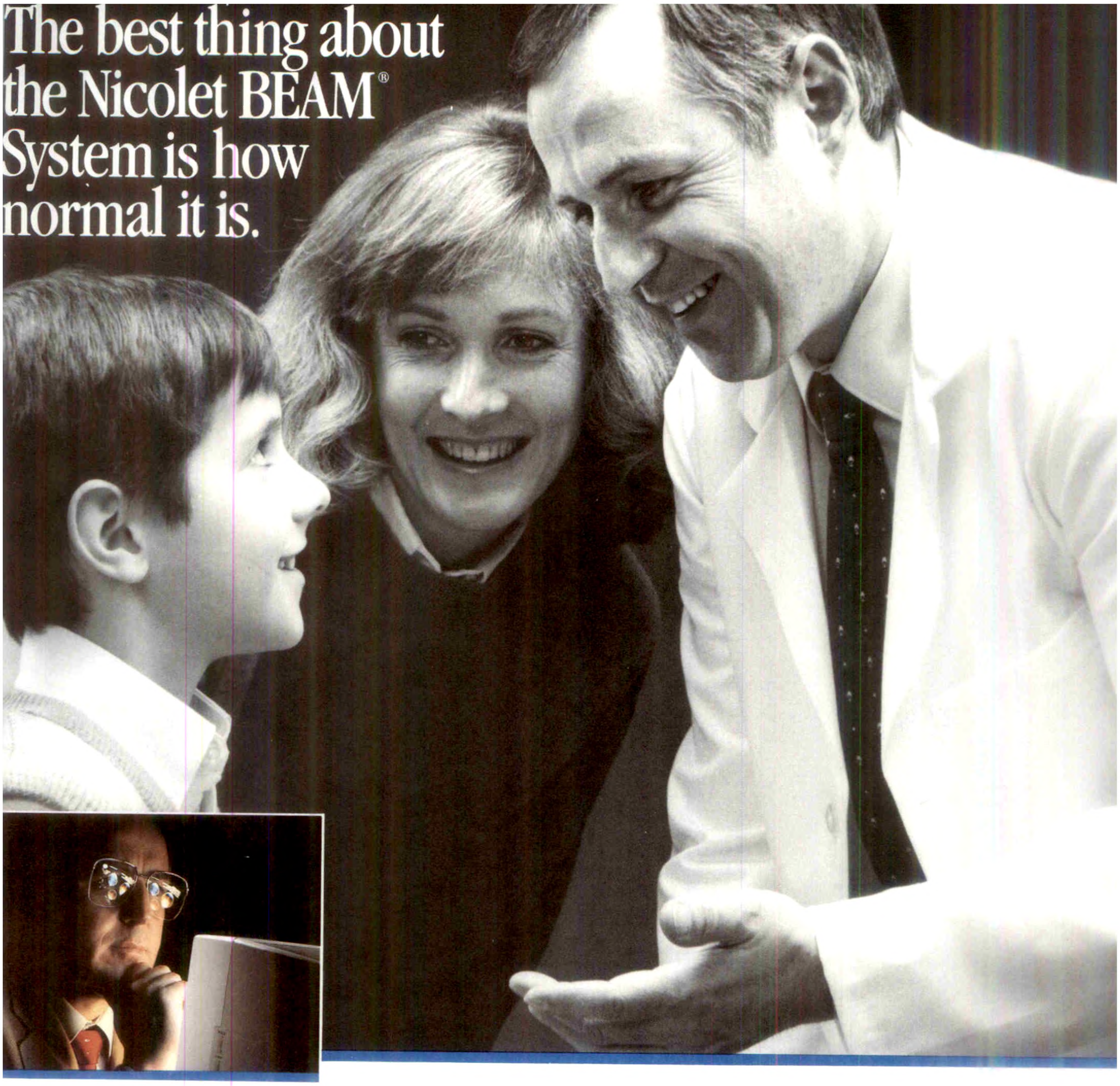
Du Pont Pharmaceuticals E.I. du Pont de Nemours & Co. (Inc.) Wilmington, Delaware 19898



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BEAM gives you sights that lead to insight. And makes you more productive, more thorough than ever before. For more information on how the BEAM System is revolutionizing neurology and psychiatry, call today.

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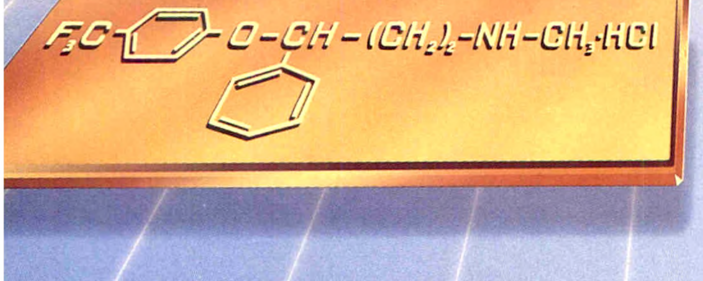

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The first highly specific…highly po blocker of serotonin uptake

Effective treatment for depression

Fewer side effects to disrupt therapy

Side effects with Prozac® (fluoxetine hy chloride) are generally mild and mana and include nausea, nervousness/anx and insomnia

Rash occurred in 4% of clinical trial p

Wide margin of safety

20-mg once-a-day therapy

Please see following page for brief summary of prescribing information.

DISTA

Please send me complete product information on Prozac® (fluoxetine hydrochloride)

NAME MD

ADDRESS

CITY

STATE ZIP CODE

Return to: Dista Products Company
P.O. Box 5321
FDR Station

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Rash and Accompanying Events*—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substanccs. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

	Percentage of Patients Reporting Event	
Body System/ Adverse Event*	Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

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*Events reported by at least 1% of Prozac patients are included.
—Incidence less than 1%.

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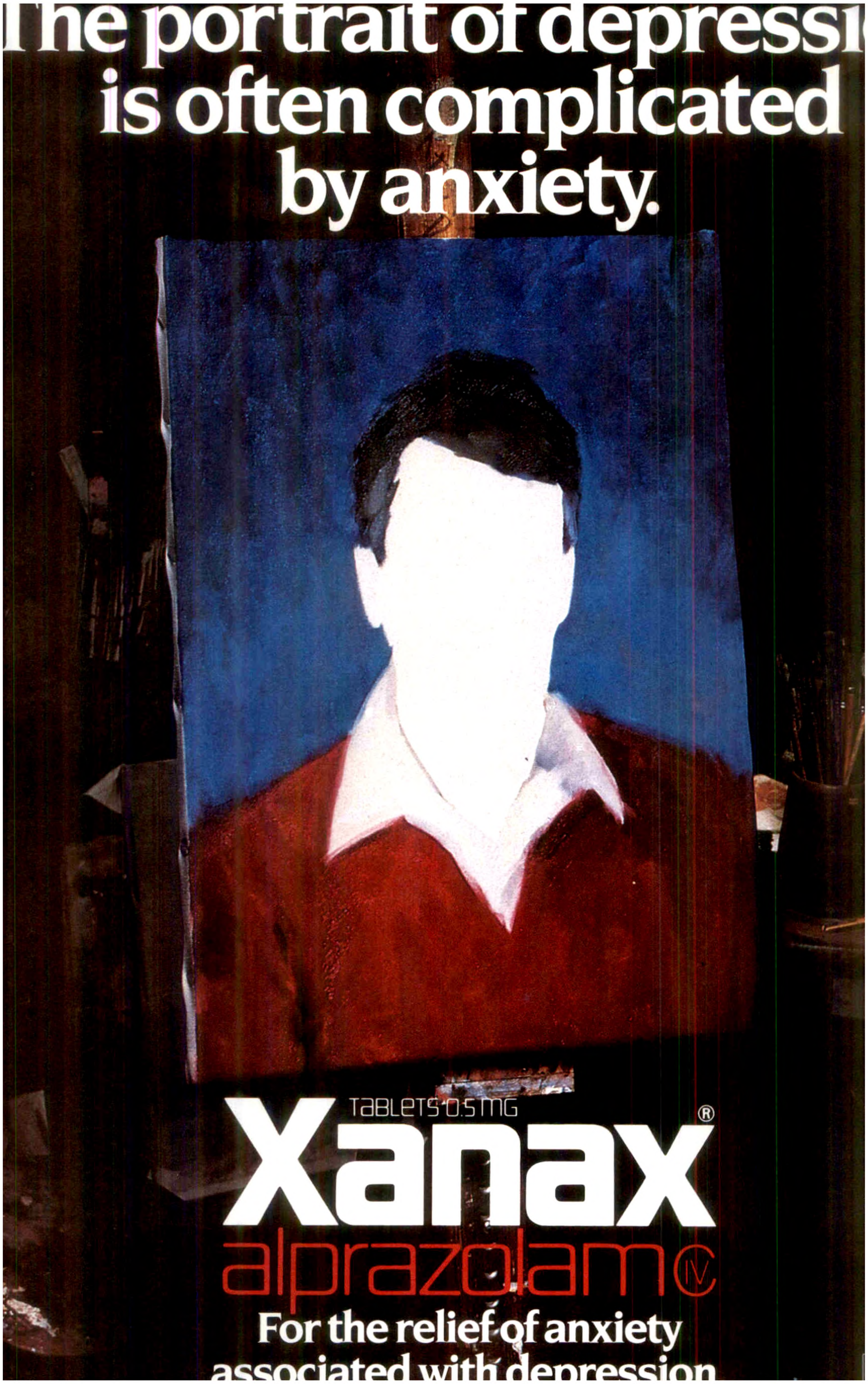

The portrait of depressi
is often complicated
by anxiety.

TABLETS 0.5 MG

Xanax®

alprazolam CIV

For the relief of anxiety
associated with depression

XANAX® Tablets
(alprazolam) ©

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.
Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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CONTACT:

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Suicide in adults, adolescents, and children.
Physical illness.
Sexual dysfunction.
Alcoholism.

These are just a few of the consequences of anxiety that will be discussed at a special program to be held at the 141st Annual Meeting of the American Psychiatric Association.

Consequences of Anxiety

Sunday, Monday, and Tuesday
May 8, 9, and 10, 1988
6:30 AM Registration and Breakfast
7:30-8:30 AM Symposium
Le Grand Salon
The Queen Elizabeth, Montreal, Canada

Sponsored by the UCLA
Department of Psychiatry
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ROGRAM
hairman
obert O. Pasnau, MD
rofessor
epartment of Psychiatry and Biobehavioral Sciences
CLA School of Medicine
os Angeles, California
ast President, American Psychiatric Association

unday, May 8
pening Comments
ouis Jolyon West, MD
rofessor and Chairman
epartment of Psychiatry and Biobehavioral Sciences
CLA School of Medicine
irector, Neuropsychiatric Institute
os Angeles, California

nxiety and Suicide
n Fawcett, MD
rofessor and Chairman
epartment of Psychiatry
ush-Presbyterian-St. Luke's Medical Center
hicago, Illinois

icide and Other Consequences of Childhood
d Adolescent Anxiety Disorders
chard E. Mattison, MD
ssociate Professor of Psychiatry
e Pennsylvania State University College of Medicine
ershey, Pennsylvania

Monday, May 9
Opening Comments
Paul Jay Fink, MD
Chairman, Department of Psychiatry
Albert Einstein Medical Center
Medical Director, Philadelphia Psychiatric Center
President-Elect, American Psychiatric Association
Philadelphia, Pennsylvania

Anxiety and Depression: A Common Neurobiological Substrate?
Steven M. Paul, MD
Chief, Clinical Neuroscience Branch
National Institute of Mental Health
Bethesda, Maryland

Anxiety and Alcoholism
Myrna Weissman, PhD
Professor of Epidemiology in Psychiatry
College of Physicians and Surgeons of
Columbia University
New York, New York

Tuesday, May 10
Opening Comments
I. A. Kapkin, MD
Assistant Professor
Department of Psychiatry
Dalhousie University, St. John Campus
St. John, N.B. Canada
President, Canadian Psychiatric Association

Anxiety and Sexual Dysfunction
Helen Singer Kaplan, MD, PhD
Director of Human Sexuality Clinic
New York Hospital
Cornell University
New York, New York

Anxiety and Physical Illness
Richard H. Rahe, MD
Professor of Psychiatry
Department of Psychiatry and Behavioral Sciences
University of Nevada School of Medicine
Reno, Nevada
President-Elect, American Psychosomatic Society

ACCREDITATION
As an organization accredited for continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association for CME requirement of the APA.

Supported by an educational grant from The Upjohn Company

*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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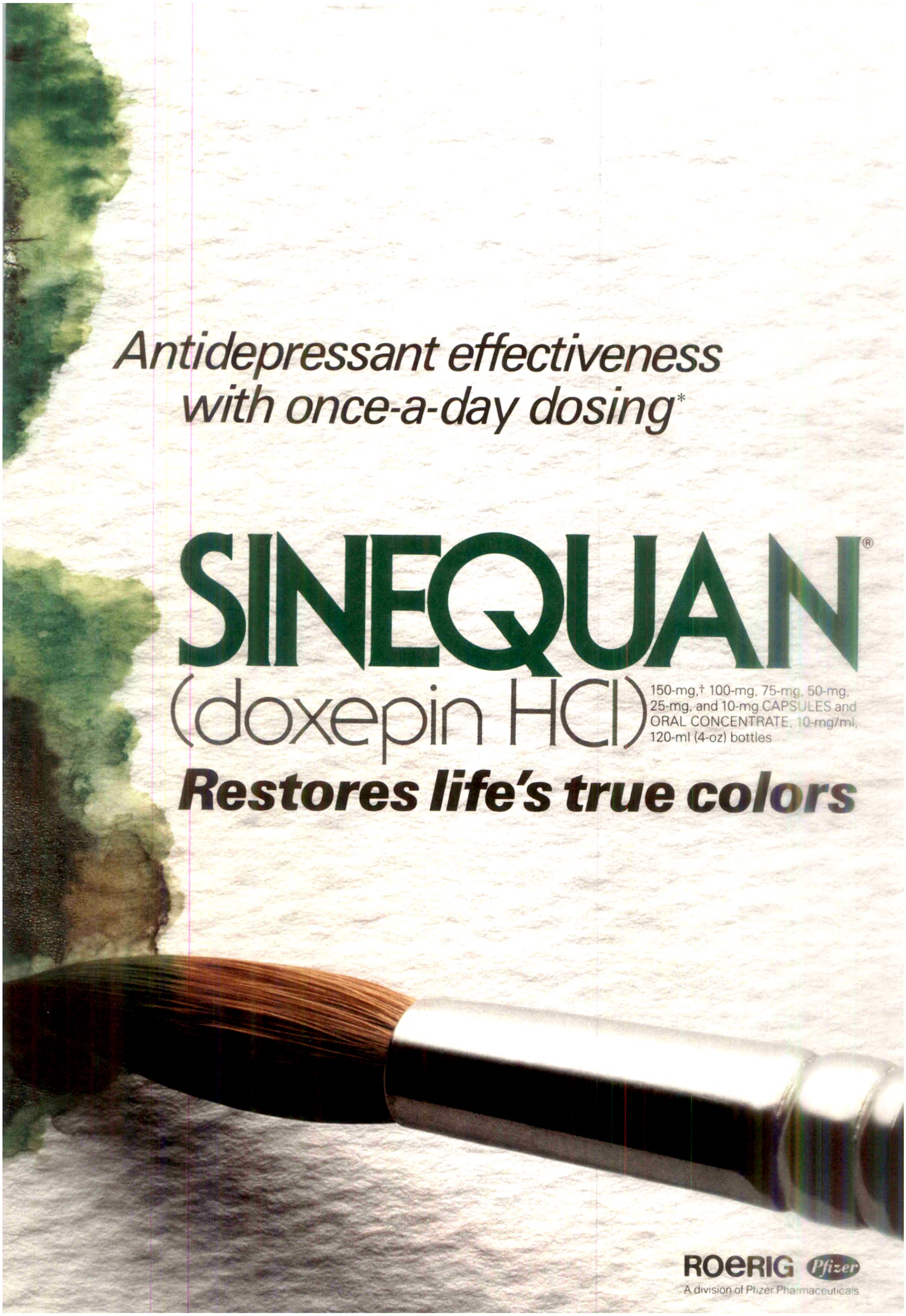

*Antidepressant effectiveness with once-a-day dosing**

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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ANNOUNCING A SYMPOSIUM

is symposium will focus on
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aiding the clinician in applying
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the diagnostic and therapeutic
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arvard Medical School
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Management of Side Effects
and Discontinuation
Professor Graham D. Burrows
Professor of Psychiatry
University of Melbourne
Heidelberg, Australia

Psychological Treatment of
Anxiety Disorders
Professor Michael G. Gelder
Professor of Psychiatry
University of Oxford
Oxford, England

Discussant
Yvon D. Lapierre, MD
Professor of Psychiatry
University of Ottawa
School of Medicine
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Accreditation

As an organization accredited for continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association for CME requirement of the APA.

Offered in conjunction with the Department of Postgraduate and Continuing Medical Education at McLean Hospital and in cooperation with the Cross-National Collaborative Study Group.

For further information, call Anxiety Disorders Symposium Coordinator at (201) 289-4700.

CROSS-NATIONAL
PERSPECTIVE ON
TREATMENT OF

ANXIETY DISORDERS

SCIENTIFIC FOUNDATION FOR CLINICAL PRACTICE

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

JUNE

June 1–3, Third Annual Guest Relations Pacesetters Conference, Philadelphia. Contact Sandra Tafler, Conference Coordinator, The Einstein Consulting Group, York and Tabor Rds., Philadelphia, PA 19141; 215-456-6354.

June 2–6, Eighth International Physicians for the Prevention of Nuclear War World Congress, Montreal. Contact IPPNW, 225 Longwood Ave., Boston, MA 02115; 617-738-9404; Telex 4430017 IPPNW.

June 5–9, 9th International Symposium on Parkinson's Disease, Jerusalem. Contact Secretariat, P.O.B. 50006, Tel-Aviv 61500, Israel; 03-65471; Telex 341171 KENS IL.

June 7–10, 38th International Trade Exhibition for Medical and Hospital Equipment and Supplies INTERFAB 88, Nürnberg, West Germany. Contact NMA Nürnberger Messe- und Ausstellungsgesellschaft mbH, Messezentrum, D-8500 Nürnberg 50, West Germany; 0911-0606-0; Telex 623613 nma d.

June 9–12, annual meeting, American Association of Neuropathologists, Charleston, S.C. Contact James M. Powers, M.D., Executive Director, 171 Ashley Ave., Charleston, SC 29452; 803-792-3581.

June 11–15, annual meeting, American Nurses' Association, Louisville. Contact Dorothy Chamberlin, 2420 Pershing Rd., Kansas City, MO 64108; 816-474-5720.

June 11–19, Twenty-Fourth Annual National Group Relations Conference, South Hadley, Mass. Contact Sheila L. Summers, A.K. Rice Institute, P.O. Box 39102, Friendship Station, Washington, DC 20016; 202-363-5443.

June 12–14, part II examinations, American Board of Psychiatry and Neurology, Kansas City, Kan. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

June 12–15, annual conference, Association for the Care of Children's Health, Cleveland. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, ACCH, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-244-1801.

June 15–17, annual conference, Children's Aid Society of Halifax, Halifax, Nova Scotia, Canada. Contact CASH, 5244 South St., Halifax, Nova Scotia, Canada B3J 1A4; 902-425-5420.

June 18–21, annual meeting, National Congress of Parents and Teachers, Salt Lake City. Contact Robert N. Woerner, Executive Administrator, 700 North Rush St., Chicago, IL 60611; 312-787-0977.

June 23–24, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Denver. Contact Fred Sierles, M.D., Program Chair, Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064.

June 26–30, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn St., Chicago, IL 60610; 312-645-5000.

June 26–July 1, annual meeting, Committee on Problems of Drug Dependence, Inc., Cape Cod, Mass. Contact Martin W. Adler, Ph.D., Executive Secretary, 3420 North Broad St., Philadelphia, PA 19140; 215-221-3298.

June 27–29, National Mental Health Consumer Leadership Training Institute, Philadelphia. Contact Paolo del Vecchio, Coordinator, National Mental Health Consumer's Conference, 311 S. Juniper St., Rm. 902, Philadelphia, PA 19107; 215-735-6367.

June 27–September 2, Ninth Cape Code Institute, Cape Cod, Mass. Contact Dr. Michael Peters, Cape Cod Institute, Albert Einstein College of Medicine, 1303 Belfer Bldg., The Bronx, NY 10461; 212-430-2307.

June 30–July 1, Rocky Mountain Conference on Neuropsychiatry and the Treatment of Persons With Developmental Disabilities, Vail, Colo. Contact JFK Child Development Center, UCHSC, 4200 E. 9th Ave., Denver, CO 80262; 303-270-8826.

JULY

July 5–7, annual meeting, Royal College of Psychiatrists, Brighton, England. Contact Vanessa Cameron, The Secretary, 17 Belgrave Square, London, SW1X 8PG, United Kingdom; 01-235-2351.

July 6–9, annual conference, Academy of Family Mediators, Portland, Ore. Contact Jim Melamed, Executive Director, AFM, P.O. Box 10501, Eugene, OR 97440; 503-345-1205.

July 10–13, ISAF Second International Congress on Adolescent Psychiatry, Geneva. Contact Mary Staples, Executive

(Continued on page A44)

When the elderly patient is taking an antidepressant, there's a chance she could end up breaking a hip.

With its low incidence of orthostatic hypotension, PAMELOR lets patients stand up with less fear of falling down.[1-5]

As you know, such falls can lead to fractures, an especially serious concern for older patients. So it's important to note that, with PAMELOR, orthostatic hypotension is relatively infrequent.[1-5] In fact, in one study, patients who stopped imipramine treatment because of repeated falls experienced no such problem when switched to PAMELOR.[3]

PAMELOR has all the effectiveness of amitriptyline,[6] as well as a low incidence of anticholinergic[1,2] and sedative[1,2,7] side effects.

So, measured by many standards, PAMELOR will help your elderly patients stand tall.

As with all antidepressants, patients with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary retention. PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly.

PAMELOR®
(nortriptyline HCl)
The active metabolite of amitriptyline

For Brief Summary, please see following page.

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The active metabolite of amitri

10 mg/ml 10 mg 25 mg 50 mg 75 mg

All the efficacy of amitriptyli

- low incidence of anticholinergic sid
- little daytime sedation[1,2,7]
- low incidence of orthostatic hypoten

References: **1.** Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. **2.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **3.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. **4.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **5.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. **6.** Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. **7.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania;

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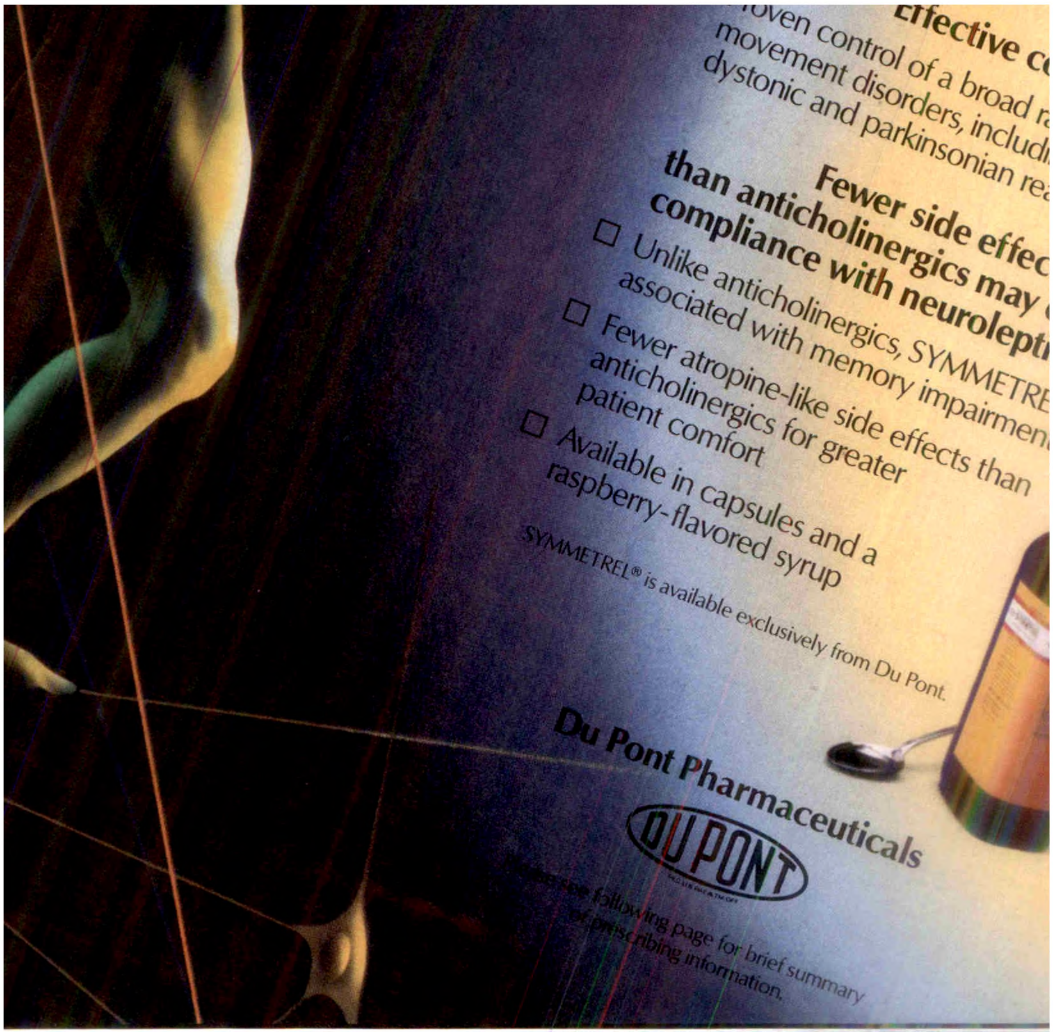

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100 MG CAPSULES
50 MG/5 ML SYRUP
(AMANTADINE HCl)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATION: Drug-induced Extrapyramidal Reactions: SYMMETREL (amantadine hydrochloride) is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with the anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The adverse reactions reported most frequently (5—10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1—5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1—1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

Bottles of 100	NDC 0056-0105-70
Bottles of 500	NDC 0056-0105-85
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As a syrup (each 5 ml [1 teaspoonful] contains 50 mg amantadine hydrochloride) in:

16 oz. (480 ml) bottles	NDC 0056-0205-16

Store at controlled room temperature (59°—86°F, 15°—30°C).

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702 and Banner Gelatin Products Corp., Chatsworth, California 91311, for Du Pont Pharmaceuticals.

References:
1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: amantadine versus benztropine. *World J Psychosynthesis* (special issue) 1984-1985; 16:40-43. **2.** McEvoy JP, McCue M, Spring B, et al: Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry* 1987; 144(5):573-577.

* D.F. Casey, *N. Engl. J. Med.* 298:516. 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

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Scientific Program 7:10 a.m.–8:30 a.m.

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TUESDAY, May 10, 1988
WEDNESDAY, May 11, 1988

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Associate Professor of Psychiatry
Director of Residency Training
Massachusetts General Hospital, Boston, Massachusetts

Monday, May 9

ALCOHOLISM AND SUBSTANCE ABUSE UPDATE

Genetics and the Risk for Alcoholism
Marc A. Schuckit, M.D.
Professor of Psychiatry
UCSD Medical School, VAMC
San Diego, California

Alcoholism Research: Implications for Clinicians
Roger E. Meyer, M.D.
Department of Psychiatry
John Dempsey Hospital
University of Connecticut
School of Medicine
Farmington, Connecticut

Update: Alcohol and Drug Disorder Treatment
Richard J. Frances, M.D.
Department of Psychiatry
New Jersey Medical School
Newark, New Jersey

Tuesday, May 10

TREATMENT OF ADOLESCENTS AND YOUNG ADULTS

Treatment of Eating Disorders
Joel Yager, M.D.
Neuropsychiatric Institute
UCLA Medical Center
Los Angeles, California

Psychodynamic Treatment of Depressed Adolescents
Jules R. Bemporad, M.D.
Massachusetts
Mental Health Center
Boston, Massachusetts

Treatment of Borderline Adolescents
James H. Egan, M.D.
Department of Psychiatry
Children's Hospital
National Medical Center
Washington, D.C.

Wednesday, May 11

SUICIDE RESEARCH AND PREVENTION

Epidemiology of Adolescent Suicide
David Shaffer, M.D.
Department of Child Psychiatry
New York State Psychiatric
Institute/Columbia University
New York, New York

Suicide Prevention in Depressed Women
Kay Redfield Jamison, Ph.D.
Washington, D.C.

What Destroys Our Restraints Against Suicide
Jonathan M. Himmelhoch, M.D.
Department of Psychiatry
University of Pittsburgh
Pittsburgh, Pennsylvania

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For Brief Summary, please see following page.

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BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. **2.** Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **3.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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(Continued from page A32)

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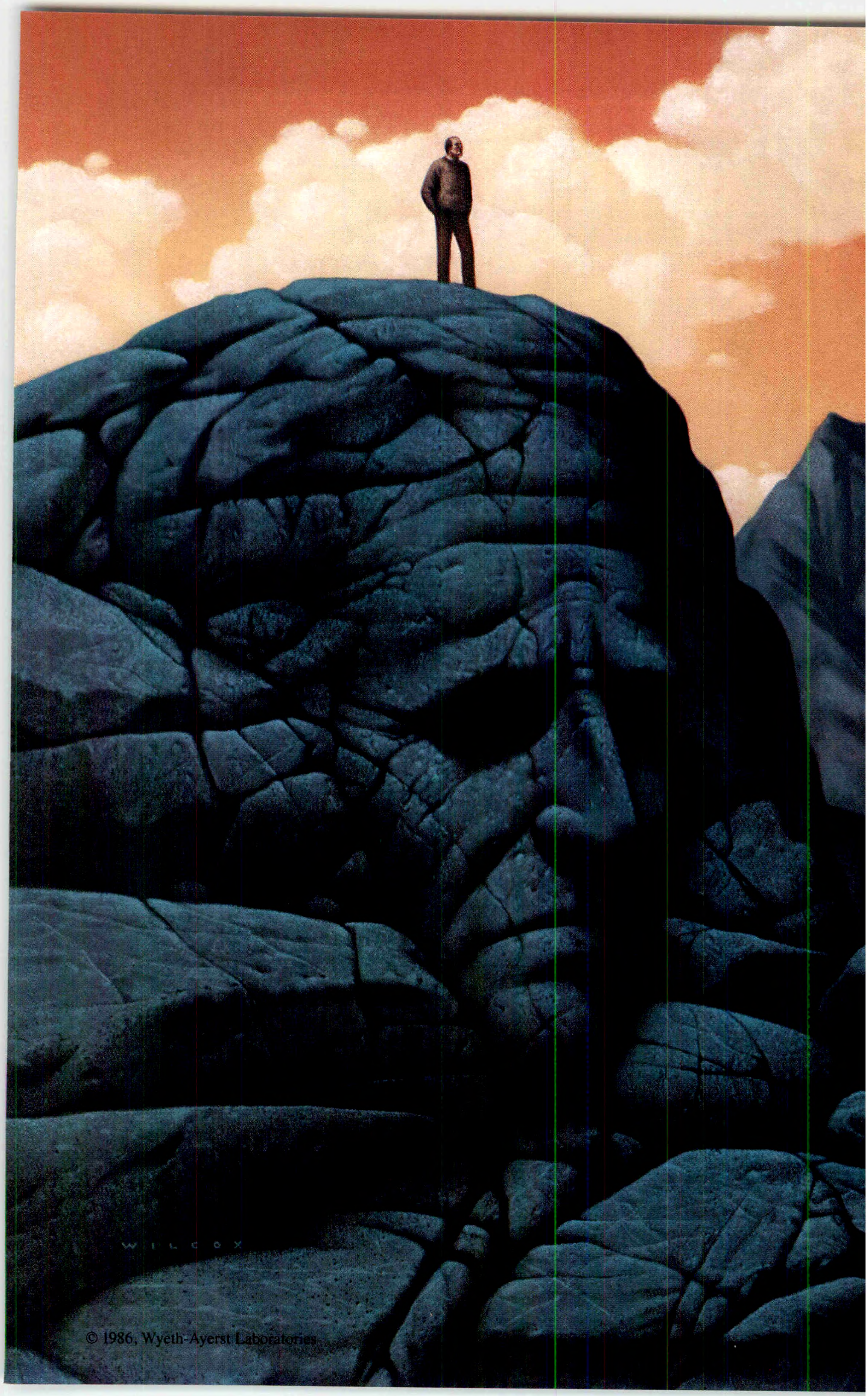

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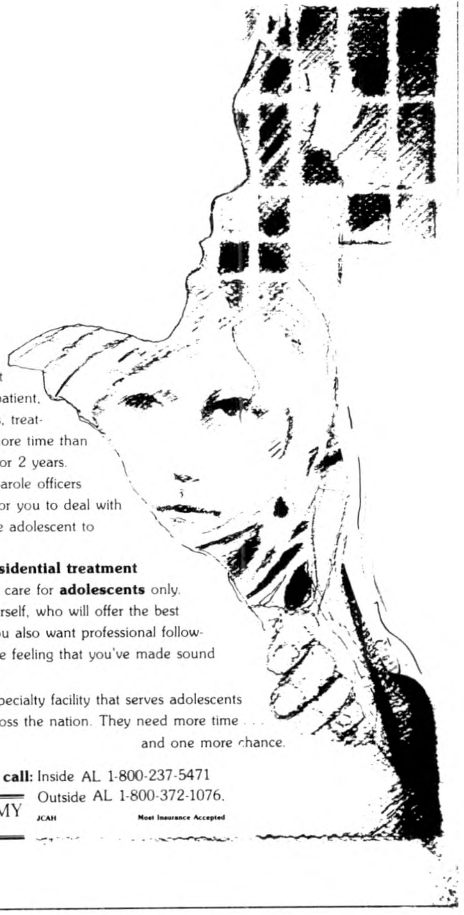

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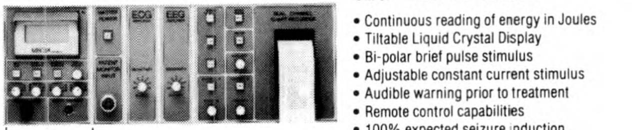

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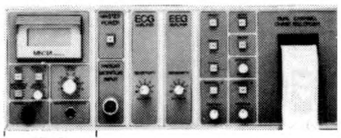

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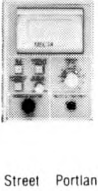

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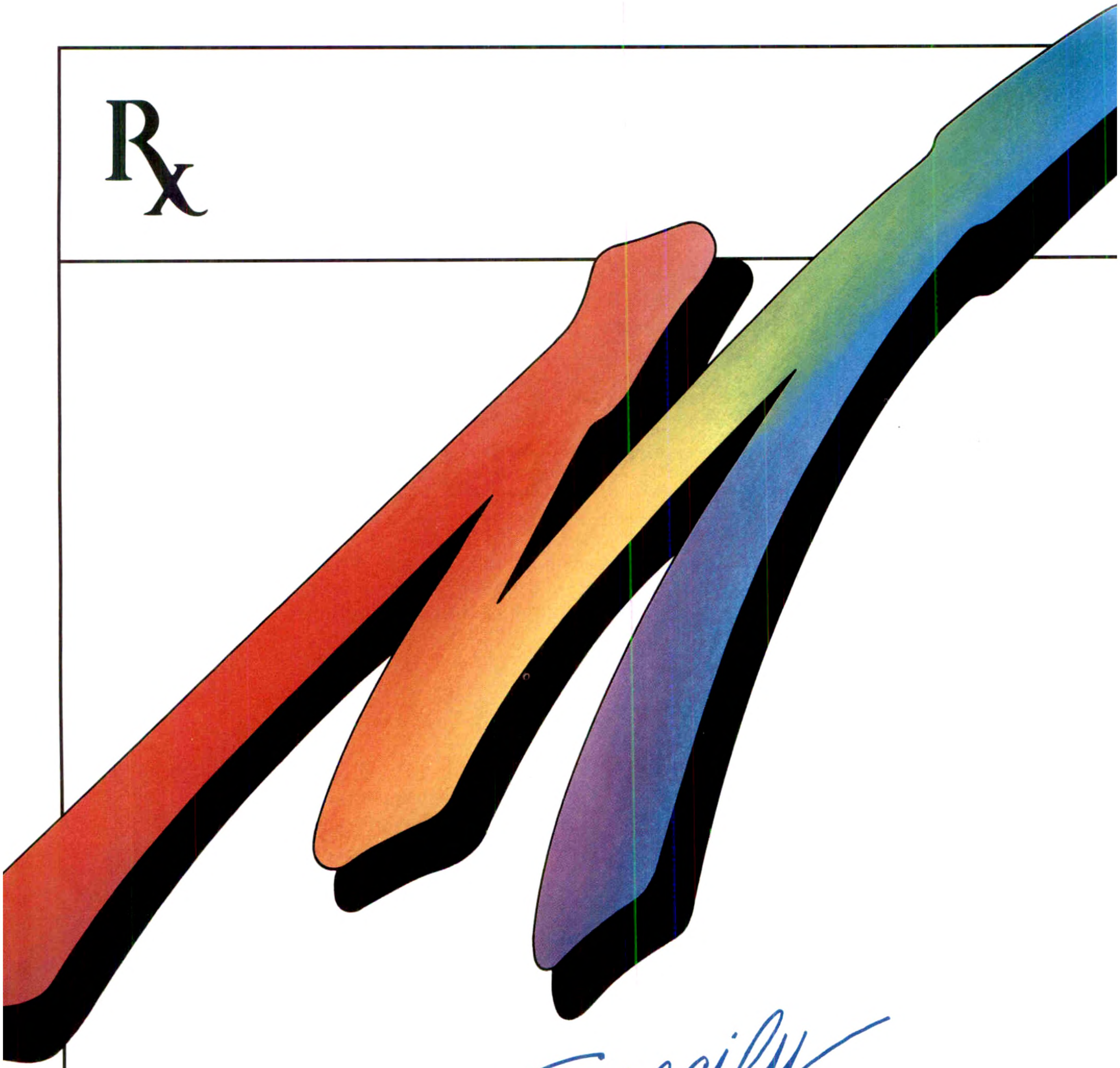

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THE AMERICAN JOURNAL OF PSYCHIATRY

The Right to Refuse Treatment With Antipsychotic Medications: Retrospect and Prospect

Paul S. Appelbaum, M.D.

The right to refuse antipsychotic medication is now more than a decade old. Its evolution has taken divergent forms, driven either by the needs of patients' treatment or the mandate of patients' rights. Regardless of the model employed, refusal is not uncommon, but refusing patients appear almost always to receive treatment in the end. These findings point up the essential illogic of allowing committed persons to refuse treatment that would permit their freedom to be restored. The future evolution of the right may proceed differently in federal and state courts, but whether at the level of legal theory or actual practice, some accommodation will restore the equivalence between the power to commit and the power to treat.

(Am J Psychiatry 1988; 145:413–419)

It has been more than a decade now since the right of committed patients to refuse treatment with antipsychotic medications appeared on the mental health scene. On April 30, 1975, three days after papers were initially filed in the case of *Rogers v. Okin*, Federal District Court Judge Joseph Tauro issued a temporary restraining order prohibiting nonconsensual administration of medication to patients at the May and Austin units of Boston State Hospital (1).

The initial order in *Rogers* attracted enormous attention in both the legal and mental health communities. Controversy grew with the trial court's 1979 opinion finding a constitutional basis for a right to refuse treatment and multiplied as courts in other jurisdictions issued similar rulings. Psychiatrists predicted the collapse of the public mental health system and warned that patients who refused medications would fill state hospital wards, "rotting with their rights on" (2). Legal advocates saw the nascent right to refuse treatment as the only hope for resurrecting crumbling state hospitals and assuring proper treatment with dignity for psychiatric patients (3, 4).

What can a decade's perspective tell us about which, if either, of these groups of soothsayers was correct? This paper responds to that question by reflecting on the evolution of the right to refuse treatment and its current status in the law, reviewing the mechanisms set up to implement the right to refuse, and assessing the options for the future. Since most law in this area continues to originate in court opinions, this paper focuses on those decisions, rather than on the secondary legislative and administrative responses (5).

THE EVOLUTION OF PATIENTS' RIGHT TO REFUSE TREATMENT

Voluntarily admitted psychiatric patients—at least in theory—have always had a right to refuse unwanted treatment, including antipsychotic medication. They have been free, given their original decision to sign themselves into a facility, to leave the hospital if treated in ways that run contrary to their wishes. In practice, of course, many voluntary patients who were too disorganized to object or to seek their release were compelled by hospital staffs, until quite recently, to accept medication which the staff believed likely to alleviate their symptoms. But when the time came for voluntary patients' right to refuse treatment to be enforced, as it did in the late 1970s, no doctrinal innovations were required, and the practice was accepted readily by mental health professionals.

Presented as the 4th Samuel and Kathryn Yochelson Lecture, Yale University, New Haven, Conn., Nov. 20, 1986. Received Dec. 16, 1986; revised May 11, 1987; accepted June 9, 1987. From the Department of Psychiatry, University of Massachusetts Medical School. Address reprint requests to Dr. Appelbaum, Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Ave. North, Worcester, MA 01655.

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Involuntarily committed patients' right to refuse treatment with antipsychotic medications was another matter. That such a right might exist was unimaginable before the 1970s. Commitment laws before 1969 had been based on criteria that emphasized prospective patients' mental illness and need for treatment (6). To commit patients because of their putative need for treatment and then allow them to refuse the very care that motivated their confinement made little sense to anyone. In that environment, the issue of a right to refuse treatment could not even be conceived.

With the massive change in commitment laws that began in California in the late 1960s, however, the assumption that commitment of the mentally ill was for the purpose of treatment began to be thrown into question. The new generation of commitment statutes, created out of a desire to limit the coercive power of the state, rejected the traditional need-for-treatment criteria for commitment on the grounds that they were vague and too broad (7). In their place were substituted criteria based on patients' likelihood of committing acts dangerous to others or to themselves or of coming to serious harm by virtue of a grave inability to care for their own basic needs (6). The treatment-oriented commitment system of the 1960s, which had survived since the 1830s, became the dangerousness-oriented system of the 1970s and 1980s.

If commitment was now for the purpose of preventing dangerous behavior, and that behavior might be controlled merely by hospitalization and observation, for the first time there was some logic in asking where the state derived the additional interest in imposing treatment on unwilling patients. Legal advocates began to inquire whether patients' rights to control what happened to their bodies—grounded in a number of constitutional and common-law theories—might not trump whatever interests the state could muster in favor of nonconsensual care.

These arguments have succeeded in an increasing number of courts in the late 1970s and 1980s (1, 8–25). No court considering a right to refuse treatment case has failed to find some substantial patient interest present. Courts have been less sympathetic to the countervailing interests of the state—including interests in safe and efficient institutional functioning, minimizing the economic burden of caring for the mentally ill, and restoring citizens to a state of mental health for their own benefit—which have often fallen before the more fundamental rights asserted on patients' behalf (26).

It is of importance to note that the U.S. Supreme Court has never directly addressed the issue of a constitutional basis for patients' right to refuse treatment. When *Rogers* finally reached the high Court after a tortuous procedural history, the Court refused to decide the case, remanding it for ultimate decision by the Massachusetts Supreme Judicial Court on state law grounds (27). The second case to reach the high Court was *Rennie v. Klein*, a New Jersey case (12). Again the Court declined to issue a specific ruling, remanding the case to the Third Circuit Court of Appeals for reconsideration in light of the recently decided case of *Youngberg v. Romeo* (28). In *Youngberg*, the Court had recognized patients' interest, grounded in the Fourteenth Amendment, in freedom from harm and unnecessary restraint but found that interest satisfied by the exercise of professional judgment to those ends, without external medical or judicial review (28). The remand may have constituted a strong hint by the Court that the right to refuse antipsychotic medication should be dealt with similarly, but the Court's reluctance to say so explicitly left the lower courts free to take other positions.

The lower courts have taken advantage of this freedom to fashion quite different approaches to refusal of treatment. In fact, to talk generically of *the* right to refuse treatment obscures the fact that there is no single right. The theoretical bases on which rights have been premised vary enormously among jurisdictions, leading to fundamental differences in the substantive rights themselves. Diversity has been further enhanced by the variety of means established for enforcing the rights, and these variations often have played pivotal roles in defining the limits of these rights. To understand the status of patients' right to refuse treatment today, we must pay careful attention to these variations. They not only tell us about the agendas underlying the creation of a right to refuse treatment but also provide a basis for thinking about the future of patients' right to refuse treatment.

DEFINING A RIGHT TO REFUSE TREATMENT: THE VARYING JUDICIAL APPROACHES

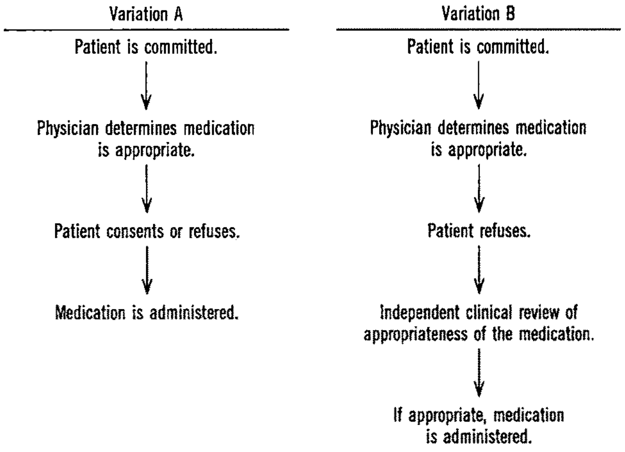
Judicial decisions on the right to refuse treatment fall into two distinct categories: treatment-driven and rights-driven models.

The Treatment-Driven Model and Its Variations

The first set of approaches can be subsumed under the rubric of a treatment-driven model (see figure 1). In this model patients' interests are limited, by definition, to the receipt of appropriate psychiatric care. Variation A of this model reflects the situation that existed before the promulgation of a right to refuse treatment. The rationale for this traditional approach was that commitment itself was based on a judicial determination that individuals' rights should be abrogated for the purpose of treatment, and this determination provided sufficient warrant for administration of medication, as well. The treating physician was presumed to know better than anyone else what treatment the patient required. Thus, a physician's determination that treatment was needed was sufficient to justify its administration, regardless of patients' wishes.

Variation A may survive to this day in some states that have had neither judicial rulings nor administrative or legislative action to limit physicians' discretion

FIGURE 1. Variations on the Treatment-Driven Model of the Right to Refuse Treatment With Antipsychotic Medications


Variation A
Patient is committed.
Physician determines medication is appropriate.
Patient consents or refuses.
Medication is administered.
Variation B
Patient is committed.
Physician determines medication is appropriate.
Patient refuses.
Independent clinical review of appropriateness of the medication.
If appropriate, medication is administered.

in the administration of antipsychotic medications. Interestingly, however, three courts have found that this model is still constitutionally viable even in the face of patients' acknowledged interests in controlling medication (8–11). Each court based its ruling, at least in part, on the U.S. Supreme Court's decision in *Youngberg v. Romeo* (28), which limits patients' interests to the exercise of professional judgment.

Variation B (see figure 1) on the treatment-driven model extends patients' interests in the receipt of appropriate care to include independent review of the treatment being offered. This approach has been adopted administratively in a number of jurisdictions, and all three court decisions upholding this variation were based on challenges to proposed or actual state regulations. Again, these courts looked to *Youngberg v. Romeo* for guidance, finding a variety of review procedures acceptable to ensure that *Youngberg*'s professional judgment standard was being applied, including internal review by a facility's medical director (12), internal review followed by appeal to officials in the state department of mental health (14), and physician discretion during the first 14 days of hospitalization, following which patients' objections would trigger internal and external review focused primarily on the appropriateness of treatment (13).

The treatment-driven model is so called because, having acknowledged the existence of some patients' interests in controlling medication, courts adopting this approach limit those interests to ensuring that the medication is appropriate for the patients' needs. Thus, treatment desiderata are primary. In fact, one might suspect (with support from some off-the-bench comments from involved judges [29]) that improvement of the quality of care in psychiatric hospitals—particularly state facilities—is more of a motive behind judicial decisions that employ this model than is any abstract desire to uphold patients' rights to liberty, privacy, or autonomy. Clinicians are generally supportive of this approach because they share these goals and because this model limits outside review of their behavior, maximizing the likelihood that patients will ultimately receive needed treatment. Administrators favor it because the few procedures required can generally be accomplished quickly and at little cost.

On the other hand, this model is unsatisfactory to many advocates of a right to refuse treatment because it continues to deny competent patients the right to make the ultimate decision about their care. Since competent, noncommitted persons usually are allowed to make such decisions, this differentiation implies to many people concerned with patients' civil liberties that committed patients are being treated unfairly in this regard. The second model for protecting patients' interests attempts to meet these objections by limiting involuntary treatment.

The Rights-Driven Model and Its Variations

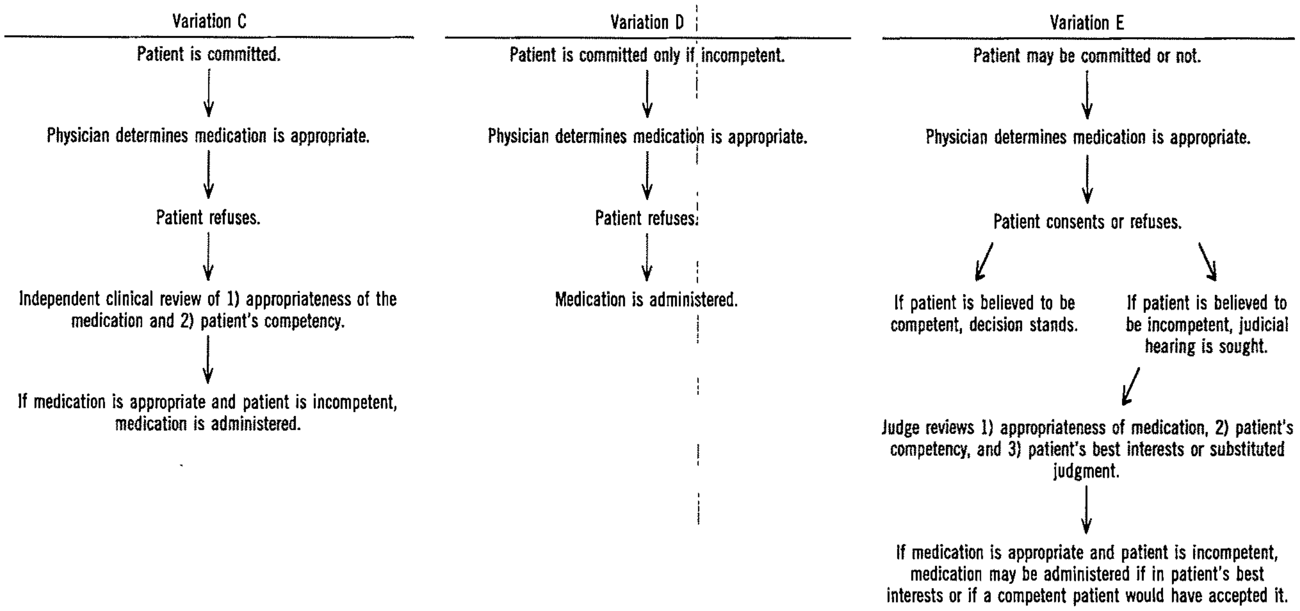
The rights-driven model is concerned not merely with patients' receipt of appropriate medication but also with the right of competent patients to control the care they receive (see figure 2). In this latter respect it is derivative of the basic assumption in our society that all competent persons have the right to control intrusions on their bodies (30). This principle is the basis for the common-law doctrine of consent and the more recently elaborated doctrine of informed consent (31). In effect, one can view the rights-driven model as an effort to extend informed consent law to the committed mentally ill, a group previously exempt from its requirements.

Variation C of the rights-driven model (see figure 2) is procedurally the simplest. Although the courts endorsing this model require that a formal exception to the requirements of informed consent exist—that is, except in emergencies, the patient must be incompetent to make a decision about treatment—they allow that determination to be made by a nonjudicial, often clinical, decision maker (15–17, 22). A finding that the proposed treatment is otherwise appropriate must also be made.

Variation C differs from the previously described approaches in raising the possibility that some patients who have been committed and objectively can be said to require medication may not receive that treatment because they have been judged to be competent. This possibility is troubling to clinicians, who worry about what they can do with such patients. On the other hand, the retention of decision-making power in clinical hands is generally reassuring to psychiatrists and administrators. This approach is generally not difficult for them to learn to live with.

Legal advocates, as might be expected, are somewhat more suspicious of this variation. They argue, correctly from a theoretical perspective (32), that competence is a legal and not a clinical construct. Clinicians are believed to have neither the information necessary to apply legal standards of competence nor—somewhat more controversially—the ability to

FIGURE 2. Variations on the Rights-Driven Model of the Right to Refuse Treatment With Antipsychotic Medications


Variation C
Patient is committed.
Physician determines medication is appropriate.
Patient refuses.
Independent clinical review of 1) appropriateness of the medication and 2) patient's competency.
If medication is appropriate and patient is incompetent, medication is administered.
Variation D
Patient is committed only if incompetent.
Physician determines medication is appropriate.
Patient refuses.
Medication is administered.
Variation E
Patient may be committed or not.
Physician determines medication is appropriate.
Patient consents or refuses.
If patient is believed to be competent, decision stands.
If patient is believed to be incompetent, judicial hearing is sought.
Judge reviews 1) appropriateness of medication, 2) patient's competency, and 3) patient's best interests or substituted judgment.
If medication is appropriate and patient is incompetent, medication may be administered if in patient's best interests or if a competent patient would have accepted it.

apply them objectively. These advocates favor an even more stringent rights-driven approach, with determinations of incompetence made only by the courts, as is ordinarily the case with noncommitted persons. Two sets of procedures have been established to accommodate those concerns.

In variation D (see figure 2), this problem is addressed at the time of the initial commitment hearing by building an incompetence requirement into the commitment criteria. In other words, only persons found by the judge at the commitment hearing to be incompetent can be hospitalized. Two courts have upheld this approach (18, later overruled by *Rivers v. Katz* [20]; 33).

Generally, this variation has strong support from clinicians. In limiting hospitalization to incompetent patients, it removes the troubling possibility that some committed patients might need treatment but not receive it. For this reason among others, the APA has endorsed variation D in its Model Law on Civil Commitment (34). The similarity between variations D and A should also be noted. Each lodges complete discretion in the treating psychiatrist once the patient has been committed. Thus, despite its novel competence requirement, variation D actually produces little change in the postcommitment status quo.

This, perhaps, has been one of the major obstacles to its acceptance, since even with APA endorsement only Utah and, quite recently, Kansas have adopted this approach (35). (An attempt to institute this approach in Florida was struck down on state constitutional grounds; the committing courts were held not to have the authority to make competency determinations [36].) Since establishing some control over physicians' decision making has been a prime goal of many advocates of a right to refuse treatment, physicians are understandably unenthusiastic about this variation. Concern over the effects on a commitment system of eliminating competent but dangerous persons from its jurisdiction may also limit acceptance of this option (37).

All of the variations thus far discussed retain some distinctions between the standards and/or procedures applied to committed and noncommitted persons. The former are deemed to have lost some measure of protection for their right to determine their own treatment. The diminution in these protections varies, but its presence is constant, a fact that troubles those concerned with patients' civil liberties (38). The final approach to be considered, variation E (see figure 2), resolves this tension by eliminating commitment as a factor in determining whether patients' refusals of treatment should be upheld.

Patients' competence is the primary criterion assessed in variation E. The competence of committed patients is assessed by procedures identical to those applied to noncommitted, allegedly incompetent patients. Competent committed patients are allowed to make their own decisions, just as they would if not committed. Incompetent committed patients have surrogate decisions made by procedures that resemble those used for other incompetent persons.

Courts in five states have insisted that this approach is required by either state or federal constitutions or state common law (19–21, 23, 24). All require that committed patients have full-fledged, judicial hearings on their competence before their refusals can be turned aside. Lawyers are provided for patients, and all procedural rules, including the right to appeal the court's determination, apply. One court ruled that once a determination of incompetence is made, a guardian must be appointed to decide whether to consent to or refuse treatment (19). The other four courts, in all but one case the highest courts in their states, held that antipsychotic medication was a treatment of such potential intrusiveness that the decision about its use could only be made by a judge. This is in keeping with traditional limitations on the rights of guardians to consent to extraordinary forms of care (39). Each court established different standards to govern the determination about whether treatment should be given.

Variation E represents an attempt to apply the informed consent doctrine to the treatment of the committed mentally ill with no concessions to any differences induced by their commitment status. In fact, one court explicitly premised its adoption of variation E on the grounds that differentiating between patients on the basis of whether or not they have been committed violates involuntary patients' right to equal protection under the law (23). For a number of reasons, this approach has been the focus of the greatest invective on the part of clinicians (40). First, alone among the approaches, it expresses distrust of the ability of clinicians as a group to make decisions that are objectively in patients' best interests. Second, the judicial opinions requiring this variation have been overtly hostile to the use of antipsychotic medications to a degree that many psychiatrists believe is unwarranted by the facts relevant to their use (41). Third, the substantive standards and procedures are designed in most cases to minimize the likelihood that refusing patients will receive treatment, increasing the probability of psychiatrists having to care for severely ill, committed patients who can be neither discharged nor treated.

On the other hand, variation E is clearly the most consistent with the law of informed consent, as long as commitment itself is not seen as creating an exception to the doctrine's requirements. Rigorous logic has an unquestionable appeal, and the decisions supporting this variation have been uncompromising in their analysis of the application of an informed consent model to this area. Variation E is more supportive than any other approach of the right of patients (in some states, even of incompetent patients) to have their wishes concerning treatment respected.

PATIENTS' RIGHT TO REFUSE TREATMENT: RETROSPECT AND PROSPECT

How can we assess the relative merits of these differing approaches to the right to refuse treatment, premised as they are on such disparate views of the purposes of civil commitment? One useful approach may be to examine the consistency of the models, with the overall purpose of involuntary hospitalization. The rights-driven variations run into serious problems here. If mentally ill persons can be deprived of liberty in circumstances in which nonmentally ill persons cannot, the basis for their being handled differently must reside in the fact of their mental illness. The only apparent justification for mental illness making a difference lies in the potential for treatment. Deprivation of liberty of the mentally ill rests on the prospects that their disorders will be treated—benefiting both society and the patients themselves—and that treatment will allow them to be restored to freedom. This argument applies both to mentally ill persons who are dangerous to others, for whom confinement without treatment would be nothing more than preventive detention, and to those who are dangerous to themselves. In the latter case, indefinite confinement is probably a more severe deprivation of liberty than a limited period of treatment with medication; if society has the right to impose one, a fortiori it must have the right to impose the other.

There is a common-sensical appeal to the idea that the state should not be hospitalizing mentally ill people against their will unless it intends to treat them. This attitude is reflected in the almost matter-of-fact statement by the *Stensvad* court (which embraced variation A): "Nonconsensual treatment is what involuntary commitment is all about" (10). Interestingly, the empirical data suggest that even when appellate courts have failed to recognize the logic of this position the ultimate decision makers are less immune to its attractions. Perhaps it is not surprising that when clinicians and administrators (variation C) review patients' refusals and ostensibly assess their competence, they are overwhelmingly likely to grant permission for treatment to proceed. In Oregon, for example, where an independent psychiatrist provided review, 95% of refusals were turned aside (42). In an Ohio forensic hospital, where a medical director applied a less stringent form of variation C (with a diluted competence criterion), 75% of refusals were overridden (43). The study showing the highest rate of refusals that were supported came from Minnesota, where an interdisciplinary board used variation C and rejected only 17% of refusals (44). Rates of rejected refusals in other studies have ranged up to 100% (45). When physicians act as judges, they still tend to think like physicians.

More impressive are the figures from Massachusetts, a variation E jurisdiction, on the rates at which judges overturn patients' refusals. One need not be entirely cynical to question whether more than 90% of refusing patients brought to court in Massachusetts are truly incompetent and would, if competent, decide to accept medication (Massachusetts law allows judges to authorize treatment only if both conditions exist), as was found in two studies (46, 47). It seems more likely that some of these patients are competent, but that once persuaded that adequate treatment will be provided, judges are willing to authorize that treatment. Anecdotal reports from my colleagues in Massachusetts confirm that review hearings tend to focus on the appropriateness of treatment rather than patients' competence. When judges are forced to act as physicians, they, too, tend to think the way physicians do.

The ironic result of the difficulty that both front-line decision makers and some appellate courts have in allowing committed patients to refuse appropriate care is that patients' right to refuse treatment has been not nearly so hard for clinicians to live with as they had feared. Rather than the anticipated epidemic of refusals, studies of clinically significant refusals (i.e., those that have reached some sort of review process) show that 1%–15% of patients will be refusers, with most studies' rates in the range of 10% (48). But, regardless of the criteria or procedures applied, 70%–100% of refusals that reach the review process are overridden (48). Psychiatrists, themselves so sensitive to the emotional difficulty of withholding help from someone in distress, underestimated the problems courts and their surrogates would have in acting similarly. Yet, the empirical data are unequivocal: the vast majority of refusing patients who reach review, even under rights-driven models, ultimately get treated.

The treatment-driven model of a right to refuse treatment is clearly more in accord with these sentiments and certainly makes more sense than the rights-driven model as far as the theory of civil commitment is concerned. Under this approach no patient would be committed and then allowed to refuse appropriate care. Within the treatment-driven model, however, there are substantial reasons to favor variation B—which incorporates independent review of the appropriateness of care—over the traditional variation A. Placing unbridled discretion in the hands of a single clinician has often led to unskillful and at times unfortunate use of medications. This is particularly true in some of our public facilities, which historically have had difficulties recruiting and supporting competent clinicians. Unfortunately, in some areas those problems continue today. If we truly believe that committed patients have the right to receive adequate care—whether we attribute the right to their Fourteenth Amendment interests or to some other source—the independent review model of variation B provides essential protection for that right.

In fact, from a treatment-driven orientation, variation B may not go far enough. Why should a patient have to refuse treatment before independent review takes place? Are more passive patients to be punished for their compliance? Ideally, all important treatment decisions should be subject to independent review, as they are today in our finest teaching institutions, where attending psychiatrists, consultation services, and conferences with outside clinicians serve that function.

A side benefit of independent review ought to be noted. Independent inspection of psychiatrists' treatment decisions, particularly when conflicts with patients arise, ought to encourage them to take patients' objections seriously and to seek to negotiate appropriate resolutions to conflicts. Patients refuse medications for a variety of reasons, some legitimate and many with important clinical implications (49). Moving away from a rights-driven model, in which each side tries to defeat the other in the legal arena, should help to focus clinicians' attention on these clinical concerns.

What is the future of a right to refuse treatment? That question must be answered on several levels. In recent cases, the trends have differed in the federal and state courts. Federal courts have tended to see treatment inherent in commitment and to follow the lead of the U.S. Supreme Court in *Youngberg v. Romeo* in adopting a treatment-driven model consisting of variation A or B. State courts, on the other hand, are free to make their rulings on independent state law grounds and increasingly are taking a different approach than the federal judiciary. Applying common-law principles of informed consent, they are opting in many cases for variation E, sometimes supplanting more treatment-driven decisions of the federal courts (20, 23). In the short term, there is no reason to believe that these trends will not continue.

Over the long haul, however, the tensions in the mental health system evoked by the presence of different criteria for commitment and for treatment cannot be tolerated. Some courts will recognize this and adopt a treatment-driven model. If other courts continue to be drawn to the rights-driven model by the logic of the common law of consent, one of two possibilities exists. Either legislatures in those states will alter commitment criteria, as in variation D, to make committability and treatability synonymous, or the appellate court decisions will continue to be undercut by on-the-scene decision makers, who will focus on appropriateness of treatment criteria.

Both sets of soothsayers turn out to have been wrong about the effects of a right to refuse treatment. Psychiatrists who feared collapse of the mental health system, as well as legal advocates who thought committed patients would be empowered to make their own treatment decisions, misjudged the real impact of a right to refuse treatment by underestimating the imperative to treat committed patients that most decision makers would feel. The movement to create the right to refuse treatment will undoubtedly continue but will inevitably evolve in a fashion that minimizes the tensions associated with the disjunction between commitment and the power to treat.

ADDENDUM

As of the end of 1987, six additional court decisions on patients' right to refuse treatment were issued. For the most part, they followed earlier trends. Three state courts adopted rights-driven, variation E approaches (50–52), while one federal court endorsed a treatment-driven, variation A system (53). An intermediate-level state court in Minnesota issued an opinion, now under appeal, that accepted an existing variation C system with a multidisciplinary treatment review panel (54). An anomalous decision from Indiana's highest court adopted a treatment-driven standard ("the necessity of medication with antipsychotic drugs") but required judicial review before administration of involuntary medication (55, which overruled 11).

Finally, the U.S. Fourth Circuit Court of Appeals, considering the rights of a pretrial prisoner in a correctional medical center, directly challenged the analysis that has dominated other federal court decisions (56). The court questioned the applicability of *Youngberg v. Romeo* to resolving disputes over refusal of treatment; the court used language suggesting that it would rule similarly in cases involving ordinary treatment settings. This case, if appealed, may provide a basis for the long-awaited U.S. Supreme Court ruling on this issue.

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Empathy: Misconceptions and Misuses in Psychotherapy

Howard E. Book, M.D., F.R.C.P.(C)

The frequent misconceptions and misuses of empathy that occur during psychotherapy are related to confusion about the definition of empathy, misunderstanding of the difference between the process of empathy and the therapist's response of being empathic, countertransference exploitation of empathy to act out the therapist's needs, the therapist's unawareness of the "layering" phenomenon, and overlooking the patient's level of self-other differentiation. These misuses result in the patient's feeling misunderstood and damaged, with a subsequent weakening of the therapeutic alliance and, at times, a breakdown in self-other differentiation. Once identified, misuses should be addressed and explored in psychotherapy to offset disruptions in treatment.

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The past decade has seen a resurgence of interest in empathy as an explorative and curative force in psychotherapy. In part, this reflects the impact of the self psychology school. From their perspective, empathy is fundamental to the emergence of certain essential transferences, the evolution of which is necessary for the curative force of that treatment approach (1–4).

This paper, however, covers the importance of empathy from a broader perspective. It explores misconceptions and misuses of empathy in psychotherapy. These observations arise from my own work as a psychoanalytically oriented psychotherapist as well as from supervising residents in their treatment of patients with character disorders or psychosis.

Empathy is an essential ingredient in the psychotherapy of both the better functioning patient and the patient who functions intrapsychically at a more primitive level. With the healthier patient, aware of his or her inner world and able to communicate it to the therapist, the empathic approach furthers the development of the therapeutic alliance (5). Research has shown a correlation between the ease with which the therapeutic alliance is established and a positive outcome in psychotherapy (6). With more severely dysfunctional patients, such as those with borderline difficulties or schizophrenic reactions, empathy is particularly important in gaining access to the patient's inner world—a world the patient may be unaware of or, if aware, unable to conceptualize or verbalize (7). A brief vignette:

> Asked to consult about a complaintive and somatizing housewife, I was unprepared for the psychotic woman sitting opposite me. With eyes darting and shoulders hunched, she began writhing, pinching her arms, and sobbing tearlessly. Occasionally, she would shout, "No, No! Not again!" Ill-prepared, I felt nervous, and to defend against my nervousness, I quickly began doing a mental status examination. The patient behaved as if I were not present.
>
> After a while my nervousness receded, and I was able to feel comfortable enough to sit with this woman and observe her and my own feelings in her presence. As I did, a slowly unfolding fantasy emerged into my consciousness in which I was pleasurably pinching this woman. As I tormented her in my fantasy, she would writhe with pain. Focusing on this fantasy, I realized that her twisting in anguish within my mind juxtaposed perfectly with her writhing movements in the chair across from me. Although this fantasy, in part, was born of frustration with this patient, I was more intrigued by how closely her movements in my mind paralleled her actual behavior in the chair.
>
> Thinking about this, I began to wonder about the communicative value of my fantasy. That is, perhaps she was experiencing what I was fantasizing. Or put more accurately, I thought that her terrible experience was evoking this fantasy within me—a communicative phenomenon that Buie (8) and Basch (9) have detailed and which I will outline later.
>
> Using this communicative value of my fantasy, I ultimately said something like "I have the idea you feel connected to an evil force that torments you any time you begin to tell me what is happening." She stopped rocking, sat up, and stated, "That's right. It's been going on for 10 months now. They punish me terribly when I start to talk about it." She continued talking for a few more moments before becoming quite psychotic again.

This vignette highlights the importance of empathy in gaining access to the inner world of a patient who was unable to conceptualize or verbalize her conscious inner experiences. Communicating my empathic understanding briefly offset her regressive state. Baker and Baker (5) noted that communicating one's em-

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pathic understanding often offsets the patient's sense of fragmentation; feeling more consolidated, he or she is able to experience and explore affects that were previously intolerable. Thus, for a brief time, my patient's regressive state was countered and a therapeutic alliance evolved: she felt understood and soothed and felt that I was on her side.

When appropriately communicated to the patient, empathic understanding provides an essential ingredient in the formation of the therapeutic alliance. And for most severely disturbed patients, the development of the therapeutic alliance is the first and major task of psychotherapy.

Another brief vignette:

> A 38-year-old hospitalized physician with borderline personality disorder appeared at my office raging about the rudeness she experienced from the nurses. It was clear how this sensitive woman both provoked and misinterpreted the nurses' behavior of which she complained. My comment, though, was, "It must be awful to turn to them for help, only to feel slapped in the face." "You understand," she sighed. "I thought you were going to defend them because you work together."

What happened? As I listened to her raging, I began to empathically sense not only the fury, of which she too was quite aware, but also the hurt and humiliation that this proud woman experienced unconsciously any time she turned to anyone for help. This intrapsychic experience of mine—feeling the humiliation and hurt which the rage defended against—is the process of empathy. This process of empathy is quite different from the response of "being empathic." The response of being empathic was communicating to the patient my understanding of her inner experience in a way that allowed her to feel understood and soothed.

Her experience of feeling understood and soothed strengthened the formation of the therapeutic alliance. This in turn allowed us to view what transpired between her and the nurses. Ultimately, she could understand the part she played in provoking rejection and see how her exquisite sensitivity to rejection made it difficult for her to feel gratified by anything she was given. This latter and essential exploration of the part she played distinguishes strengthening the therapeutic alliance through being empathic from merely promoting a positive transference by colluding with the patient's distortions.

From these two vignettes, I will go on to sharply compare and contrast the therapist's intrapsychic process of empathy from his or her interpersonal response of being empathic. I will then discuss misconceptions and misuses of empathy from four vantage points: the semantic, the conceptual, the countertransferential, and the technical. For the sake of clarity, misuses have been artificially organized into these four categories. In fact, there are more than these four divisions. Most important, these misuses usually overlap in psychotherapy and are not mutually exclusive.

DEFINITIONS

What is empathy? Empathy has been defined as a spontaneous, intrapsychic, preconscious, and temporary experience, having affective/cognitive components, that occurs within the therapist, whereby he or she comes to know and comprehend what the patient might be experiencing consciously or unconsciously (8, 10). As Buie (8) understands empathy, it "begins with perception of oftentimes subtle cues from the patient [through normal sensory modalities], then proceeds intrapsychically in the analyst through a particular coordinated use of certain abilities, that is, memory, fantasy, and awareness of his own feelings and impulses" (p. 283). From an analogous viewpoint, Basch (9) conceptualizes empathy as representing the emergence of a particular affective state within the therapist that reflects his or her autonomic response to the patient's appearance and behavior.

Note that, as defined, the term "empathy" means simply a particular mode of gathering data about the internal experiences of another (11). It makes no comment on how these data are used, whether for good or evil (5). Basch, for example, noted that "some of the world's greatest scoundrels have been exquisitely and unerringly attuned to grasping the significance of the unconscious or unspoken affective communications of others and have used that knowledge to achieve base aims. Is this too empathy? Yes it is" (9, pp. 119–120).

With the psychotic housewife, I became aware of her feeling tormented by evil forces perhaps through the pathways both Buie and Basch have described. I was empathic to her conscious experience, which she was forbidden to discuss. In the case of the angry physician with a borderline disorder, I was empathic both to her conscious rage and to her sense of humiliation and disappointment, which her rage defended against and kept unconscious.

This experiencing of the patient's conscious and unconscious emotional states is the essence of empathy and requires from the therapist the essential ability to oscillate from being observer to being participant to being observer. Jaffe (12) alluded to the significance of this oscillation when he referred to empathy requiring thinking *with* the patient and then *about* the patient. It requires an ability to be with the patient affectively and then also to think about the patient. This oscillation distinguishes empathy from identification and projection, where there is a loss of objectivity and where the function for the therapist is primarily defensive and unconscious.

Having defined empathy, how then do we define being empathic? Being empathic is an interpersonal response occurring between the therapist and the patient by which the therapist uses his or her empathy to voice comments about this patient's internal state, which results in the patient's feeling understood and soothed. Unlike empathy, being empathic has a positive valence. It refers to the therapist's using his or her empathic understanding in a manner that is helpful to the patient (5). Conversely, misuses of empathy result in a patient who feels misunderstood and assaulted and who, in turn, responds to the therapist's comments with increasing defensive maneuvers, unnecessary elaboration of a negative transference, and/or narcissistic rage responses. All of these responses can be understood not as the patient's unconscious need to sabotage treatment nor as primitive unneutralized aggressive drives but as an understandable and vengeful reaction to a nonresponsive or even hurtful environment (4, 5).

MISCONCEPTIONS AND MISUSES

Semantic Confusion

Empathy is often confused with sympathy, kindness, and approval. Thus, it may come to mean behaving compliantly in response to the patient's behavior and sympathetically to his or her problems. It may evoke a stance of unquestioning acceptance of the patient's experiences by the therapist. This unquestioning acceptance dampens the essential oscillation between the roles of participant and observer that I referred to earlier. It leaves the therapist stuck in the participant stance only. Bogged down in this stance, the therapist runs the risk of only identifying with and colluding with the patient's experience. Thus, it also represents a countertransference problem.

A short case example:

> A first-year resident, when verbally assaulted by a paranoid patient, responded, "I'm glad to see you can get your anger out." The patient hesitated, looked perplexed, and then angrily roared, "You bastard! To be so happy that I am this upset!" When asked about his comment, the resident stated, "I was just trying to be empathic."

For this resident, empathy equated with being unquestioningly accepting. Good. However, this accepting stance was not empathic. It had little to do with experiencing how frightened this patient felt unconsciously. As he and I discussed this, the resident became aware of how frightened he had been with this patient and how helpless he felt at limiting the patient's verbal attacks. His comments were defensive, born of his need to appease this patient and thus dampen his own fright.

Another brief vignette:

> A Holocaust survivor raged against the rudeness to which he felt subjected at work. His Jewish therapist responded, "It really makes me angry when I hear that. What the hell's the matter with them?" The patient responded, "That's what I'm telling you. They're all a bunch of butchers!"

The therapist, although seemingly empathic to this man's rage and sense of belittlement, in fact identified with the patient's outrage and sense of injury to the point where he could not appreciate how this man's aggressive and suspicious stance invited the very rudeness from which he suffered. The therapist lost the essential oscillation from the role of participant to that of observer and, stuck in the participant stance, was no longer empathic. In his sympathy for and identification with his patient's suffering, the therapist intensified the patient's use of denial and projection. He further diminished any awareness this patient had concerning the part he himself played in provoking the unfortunate abuse he received.

"Humoring the patient" may also be confused with empathy. However, humoring the patient is a distorted understanding of the process of empathy. It is a forced pretense that has defensive purposes for the therapist and results in the patient's feeling demeaned.

> In my presence, a second-year resident interviewed a recently admitted patient. This upper-middle-class 40-year-old woman was elegant in dress, articulate in speech, and somewhat regal in bearing. She seemed almost normal except for one symptom: she said quietly but with firm conviction that her daughter was not really her daughter but an almost identical impostor. Only she could see the imperceptible differences that convinced her that this teen-ager was not her child. After listening to her plight, the resident stated, "I guess it's awful thinking someone switched daughters on you." The patient smiled uncertainly and immediately grew silent.

Discussing this patient and his words to her, I asked the resident what he was thinking or feeling while she was talking. He replied, "It's funny; I could hear her words about her daughter being an impostor, but she seemed so normal otherwise, like anyone's mom. I found it hard to believe she really believed all this was happening. I heard her words, but I just couldn't believe she meant them."

This resident, like the therapist in the previous example, also lost the essential oscillation from the participant to the observer role and was no longer empathizing with the patient. This resident, though, was stuck more in the observer stance. Unconsciously, he could not allow the oscillation toward the participant role because, through identification, he was made too uncomfortable by his patient's otherwise normal appearance. That one could look so normal yet be so disturbed was too anxiety provoking. Thus, although he understood her words in thinking about her, his attitude reflected his defensive disbelief in thinking with her and in the existence of this patient's inner experience of perplexity at a world gone awry. He was humoring the patient.

Conceptual Difficulties

Conceptual misuses of empathy arise from a lack of clinical distinction between the therapist's intrapsychic process of empathy and his or her interpersonal response of being empathic. Although related, the two are quite different. As previously defined, empathy reflects the intrapsychic experience of the therapist by which he or she affectively and cognitively comprehends the conscious, preconscious, or unconscious experience within the patient. Being empathic is an interpersonal response by which the therapist voices empathic understanding in such a way that the patient feels understood and soothed.

Struggling for words to describe her torment, a depressed elderly woman in psychotherapy stammered, "It feels . . . like . . . ah . . . I'm . . . ah . . . under . . . a huge . . . ." At this point, her therapist, sensitive to and empathizing with this woman's desperate experience of feeling submerged and suffocating, responded, "Under a suffocating, painful weight." His patient turned away and stopped talking.

Although he was empathic to her suffering, this therapist was not being empathic to the patient. She did not experience his interruption as soothing. What one understands of a patient's internal experience and how one uses (or chooses not to use) that understanding are quite different. A test of successfully being empathic is the extent to which the therapist's responses stimulate and deepen the patient's narrative flow (13). In neither this vignette nor the previous example of the regal woman believing her daughter to be an impostor did the therapist's response deepen the narrative flow. In discussing their therapists' comments to them, both of these patients described feeling silenced and hurt.

Put another way, empathy is being able to finish a patient's sentence. Being empathic, though, is *not* finishing that sentence. Having one's sentence finished is seldom experienced as being understood or comforted but, rather, is experienced as intrusive and infantilizing (14).

Countertransferential Difficulties

Countertransferential misuses of empathy refer to the therapist's using empathy defensively to gratify his or her own needs. Commonly, these needs have to do with a wish to impress, bolster one's sense of omnipotence, or relieve one's own sense of aloneness that might be associated with treating certain patients.

For example:

A 22-year-old painter, recovering from a brief paranoid reaction, struggled to describe his psychotic experience. He said, "I feel like that character in the movie, . . . hmmm, I can't remember his name. He was also in *The French Connection.*" "Oh," I replied, "you mean Gene Hackman in *The Conversation.*" The patient winced and became painfully silent.

I was not being empathic. If I had been, I might have remained silent or perhaps acknowledged his struggle as he attempted to convey his psychotic experience. What I did was act out my antitherapeutic need to impress under the guise of being empathic.

Similarly, therapists may feel pressured to comment repetitively on what a mute patient might be experiencing. Often, this is done in order to relieve and defend against the terrible aloneness they themselves experience in the presence of such a patient. Unfortunately, this countertransference behavior does not soothe. Often, it is experienced as intrusive or distancing, and it may only force the patient to protectively increase withdrawal and ultimately accentuate his or her feelings of aloneness.

Technical Misuses

Two common technical misuses of empathy deserve comment. The first represents the therapist's disregard of the "layering" of internal experiences. The therapist does not correctly assess the relative importance of the most pressing layer of the patient's inner experience to which the therapist should attend. A patient may simultaneously experience a number of conscious, preconscious, and unconscious feelings that may resonate empathically within the therapist. It is important for the therapist to know clinically which layer of feeling to address. For example—to return to the hospitalized physician who appeared, enraged, at my door—certainly, I was aware of and could experience how angry she was. But at the same time, I also experienced how humiliating and demeaning it was for this proud woman to turn to anyone for help. For me to have responded in the context of her anger would have been less correct technically than my responding to her painful sense of having been wronged.

Good examples of this layering phenomenon are cases in which the patient finds it painful to be understood.

A 32-year-old single businesswoman, raised by an icy mother, kept herself unaware of the chilliness in her mother's responses. She denied the heartbreaking disappointment she experienced in her mother's well-meaning but crippled attempts to care for her. In one session, she recalled how, when she was a child, her mother had impulsively given away a small puppy. I murmured how heartbroken and disappointed she seemed to feel. She responded by turning on me in a fury, spitting out the words: "Don't pity me! Don't you dare pity me!"

After a number of such occurrences, I began to realize that although my empathic understanding of how crushed she felt was accurate, I was missing a more clinically relevant layer. I was overlooking how painful it was for this woman to allow these sorts of feelings to be understood. Ultimately, addressing this layer, my more clinically indicated empathic response became "I think I have some idea of how you feel, but I also know that any time I tend to understand how painful things are for you, you feel looked down on."

The second technical misuse occurs in another clinical situation, in which a patient also responds to being understood by feeling damaged, rather than comforted and soothed. Such a situation occurred with the previously described 22-year-old painter, recovering from a paranoid reaction, who struggled to talk to me about a character from a movie. He winced and became painfully silent when I identified "Gene Hackman" and "The Conversation" as the words he was trying to retrieve. He felt hurt and withdrew because he accurately perceived my countertransference attempt to show off. Later, when we further explored his experience of my words, another dynamic emerged: "When you said 'Gene Hackman' just while I was trying to recall his name, it felt like you could see my thoughts. I felt you were reading my mind. It was very frightening, just like what was happening to me when I was really sick. I didn't know what to do or how to hide myself." This man experienced my comments about his inner state as if I were reading his mind, and he reacted with fright.

What had transpired? I had not paid attention to nor empathized with the difficulties he was experiencing concerning his ability to maintain self-other boundaries. Because he was still in the process of recovering from a psychosis, his ability to firmly differentiate self from other was quite tenuous. Given these difficulties, he experienced my comments as if I were seeing through him—as if no self boundary existed around his internal experiences.

The appropriate empathic approach with patients who show this fluidity in self-other differentiation is first to address how confusing and upsetting being understood can be. For these patients, empathic comments are often best voiced as, "From your words and behavior, I think I have an idea of what you might be feeling. But I also know that you become frightened when I talk about what's going on inside you. It feels like I can see right through you, but I can't." Comments such as these offer firm reality-based structure and support self-other differentiation by explicitly detailing that the understanding comes from the patient's words and behavior and not through mind reading. Such comments also empathically acknowledge how unsettling being understood might be, given the tenuous hold these patients have on differentiating self from other.

CONCLUSIONS

In this paper I have attempted to sketch the importance of empathy in psychotherapy and highlight the common and often unacknowledged misuses to which it is put. These misuses result in a patient who, quite quickly after the therapist's comment, feels hurt, perplexed, misunderstood, assaulted, and/or fragmented. (The one exception occurs when the therapist, although believing that he or she is being empathic, is really overidentifying with the patient and colluding with the patient's scotomas. In this case, the patient may feel understood and soothed, although at the cost of diminished self-awareness.) In response to these upsetting feelings, the patient may suddenly withdraw or quickly become enraged.

Avoiding these misuses requires the therapist to have a clear understanding of the concepts of empathy and being empathic and the distinction between them, an awareness of certain countertransference responses that exploit empathy, an appreciation of the layering phenomenon, and a knowledge of the patient's level of self-other differentiation. Therapists should consider whether they may have misused empathy whenever a patient responds with withdrawal or rage. In this situation, it is ultimately very helpful to the patient for the therapist to respond to a misuse of empathy by focusing on what just transpired between him or her and this patient and attempting to respond to this misuse in a more accurate empathic, and therefore reparative, manner.

Lest this paper has oversimplified rather than clarified these issues of empathy, I would like to close with the thoughtful comment made by Shapiro (15): "That many people feel they understand or are felt to be understood is no guarantee of such understanding."

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Adverse Cutaneous Reactions to Antidepressants

Julia K. Warnock, M.D., Ph.D., and John W. Knesevich, M.D.

The authors review the literature on adverse cutaneous reactions to antidepressant medications. The prevalence of rashes ranges from approximately 2% to 4% but is higher for certain antidepressants such as maprotiline and carbamazepine. Antidepressant drug reactions result in a variety of cutaneous morphologic patterns, but the majority of eruptions are exanthematous. The patterns of these reactions are similar whether the pathogenesis is mediated by immunologic or nonimmunologic mechanisms. The management of patients with adverse cutaneous reactions to antidepressants is discussed, and various recommendations are given.

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Antidepressant medications are among the most frequently prescribed drugs in the United States. Prescriptions written for amitriptyline alone in 1982 totaled 17 million (1). Of the adverse side effects of antidepressants, dermatologic manifestations are the most common type of allergic reaction (2). The tricyclic antidepressants and monoamine oxidase inhibitors listed in appendix 1 are familiar mainstays in the pharmacologic treatment of depression. Some of the medications listed may not be readily recognized as antidepressants. As an example, carbamazepine, a tricyclic compound related to imipramine (3), is an effective anticonvulsant and is used for the treatment of trigeminal and glossopharyngeal neuralgia. Carbamazepine also has antimanic and antidepressant actions (4). While benzodiazepines are not regarded as effective in the treatment of depression, alprazolam, a triazolobenzodiazepine, has been found to have an antidepressant effect (5–8). Other antidepressants recently introduced include trazodone and maprotiline. The purpose of this paper is to review adverse dermatological reactions to antidepressant medication and to suggest some management alternatives for patients who develop such manifestations.

PREVALENCE AND EPIDEMIOLOGY

While the prevalence of skin reactions has been reported as 2.2% for most drugs (9), it appears to be higher for antidepressant medication. Litvak and Kaelbling (10) concluded that skin lesions appeared in approximately 5% of patients taking psychotropic medication. However, these authors did not describe separately the skin lesions associated with antidepressants. Maprotiline, a tetracyclic compound, has been noted to cause skin rashes more frequently than the tricyclic antidepressants (11). One author has suggested that 6% of patients receiving maprotiline suffer an adverse cutaneous reaction—a prevalence approximately twice that for tricyclic antidepressants (12). Forrest (13) noted skin rashes in 8% and 2% of his experimental groups taking maprotiline and amitriptyline, respectively. However, Stewart et al. (14) found no evidence of skin reactions in 326 hospitalized patients receiving amitriptyline. Fluoxetine has been reported to cause a skin rash in approximately 3% to 4% of the patients treated (15). Alprazolam has been documented to have adverse cutaneous effects in 4% of the patients treated (16), whereas reports of skin reactions to carbamazepine varied between 3% (17, 18) and 16.6% (19).

While epidemiological data on adverse cutaneous reactions to antidepressant medication are not known specifically, it may be possible to extrapolate from drug reactions in general. It is known, for example, that women experience cutaneous drug reactions twice as often as men (20). In addition, there does not appear to be a correlation between age and adverse cutaneous reactions (9). Drugs may produce a variety of types of skin eruptions (21). One study (22) summarized the incidence of various clinical cutaneous manifestations of drug reactions. Exanthematous eruptions accounted for 46% of the reactions, followed by urticaria in 23%, erythema multiforme in 5.4%, exfoliative dermatitis in 3.7%, and photosensitivity in 2.8%.

PATHOLOGY AND PATHOGENESIS

Adverse cutaneous eruptions due to antidepressants may be mediated either by immunologic or nonimmunologic mechanisms. The immunologic mechanism requires activation of the host's immunologic pathways. An important factor in the immune response is

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the characteristics of the drug molecule (20). Antidepressant drugs are simple chemicals with molecular weights of less than 1,000. Compounds with a small molecular weight cannot elicit an immune response unless these drugs or their metabolic products are able to combine with tissue macromolecules to form a hapten-protein conjugate. Once the covalent bond or strong electrostatic binding (23) occurs, the conjugated molecule can induce synthesis of drug-specific antibodies, while the antidepressant (hapten) alone is incapable of eliciting such antibody production (20).

In addition, nonimmunologic mechanisms can result in a cutaneous reaction. Two examples are drug interactions and cumulative toxicity (20). Basler and Goetz (24) have suggested a synergistic drug interaction between amitriptyline and minocycline leading to hyperpigmentation of the skin. A bullous skin eruption has been associated with carbamazepine overdosage (25). Brume et al. (26) described a case of mianserin-induced agranulocytosis that presented as an abscess. It is rarely possible to identify either the immunologic or the nonimmunologic mechanism involved in the pathogenesis because the mechanisms of most clinical drug reactions are unknown (20).

Other explanations of adverse cutaneous reactions to antidepressants include the excipients and additives used in the drug formulations. Tartrazine, or Food, Drug, and Cosmetic Act (FD&C) yellow number 5, a color additive, is a stable azo dye present in thousands of foods and pharmaceutical products (27), including some antidepressants. The prevalence of tartrazine intolerance in the United States is estimated to be as low as 1 in 10,000 and as high as 1 in 34; the higher rates have been noted in patients with aspirin sensitivity (28). Adverse cutaneous manifestations of tartrazine have included pruritus, urticaria, exanthematous eruptions, angioedema, and nonthrombocytopenia vascular purpura (27).

CLINICAL CUTANEOUS MANIFESTATIONS

Appendix 2 lists cutaneous manifestations that have been associated with particular antidepressants (21, 29).

Urticaria

Urticaria reflects inflammation in the superficial dermis and is probably mediated by immunoglobulin E (IgE). An antidepressant or its metabolite combines with IgE that is bound to the surface of cutaneous mast cells. This releases cell vasoactive substances such as histamine, leukotrines, and prostaglandin D_2 and precipitates the vasodilation and increased vascular permeability that contribute to the formation of hives (30). The antidepressants that cause urticaria include the tricyclics (13, 31, 32), maprotiline (33), trazodone (34), and carbamazepine. Urticaria may occur within minutes to a few hours or even days after the administration of the antidepressant medication (35).

An interesting case report documented an urticarial reaction to imipramine withdrawal. The authors (36) suggested that immunologic cAMP perturbations, possibly produced by the fluctuating tricyclic dosage during withdrawal, precipitated the eruption. IgE-cAMP interactions are considered to be possible mediators in the classical type 1 reactions (37). This observation suggests the importance of slowly tapering antidepressants that are to be discontinued, especially in patients with a history of atopic illness.

Exanthematous Eruptions

Exanthematous eruptions (also known as morbilliform or maculopapular eruptions) are often symmetrical in distribution, with erythematous macules and papules erupting initially on the upper trunk. Involvement may generalize to include the entire body, including palms, soles, and mucous membranes. Pruritus may be present, as well as mild elevations in temperature (20). The tricyclics (38), carbamazepine (39), trazodone (40, 41), alprazolam (16, 42), and maprotiline (43, 44) have been associated with this eruption. These eruptions generally occur within 3–10 days after the initiation of treatment. On occasion, the eruptions may fade and even disappear despite continued therapy.

Molnar (43), in a double-blind study, found that one of 12 patients assigned to the maprotiline treatment group developed a generalized maculopapular rash. The drug was discontinued on day 12, and the eruption gradually faded. The patient was later treated with amitriptyline, to which she responded satisfactorily and without further cutaneous reaction. In another experimental trial (44), one of 15 patients assigned to the maprotiline treatment group developed a skin rash severe enough to be withdrawn from the study.

Saraf et al. (45) examined the side effects of imipramine in children. Of 65 children in the imipramine-treatment group, 6% developed a rash and 3% developed pruritus. In the placebo group of 37 children, there were no rashes, but 5% suffered pruritus. Schulterbrandt et al. (46) found that only one of 201 patients treated with imipramine developed a skin rash serious enough to require termination from the study. Faltus and Geerling (47) noted one patient in the imipramine experimental group, which consisted of 23 patients, who developed a mild to moderate rash on the upper half of the body, the arms, and the neck. Butterworth (48) evaluated imipramine in the treatment of depression associated with alcohol withdrawal. He found that one of 20 patients in the treatment group experienced pruritus, compared with none in the placebo group. In addition, one patient in each of the two experimental groups developed a rash.

In an extensive study by Feighner et al. (6), the effects of alprazolam, imipramine, and placebo were compared in the treatment of depression. Dermatoses or allergic reactions were found in 21 of 236 patients receiving alprazolam, 26 of the 244 patients receiving imipramine, and 26 of 243 patients in the placebo group. While alprazolam may not appear to be significantly different from placebo in the Feighner study or in another series (49), Hussar (16) noted that alprazolam caused a rash in 4% of the patients studied. The eruptions associated with alprazolam appear to be mild to moderate in severity (50) and have reappeared with readministration (42). Fluoxetine, a selective serotonin uptake inhibitor, caused a "rash" in approximately 48 of 1,378 patients (15). Approximately two-thirds of these patients were able to continue treatment without difficulty; however, one-third discontinued therapy because of the dermatologic side effects. Some patients required steroid treatment, but all were reported to have recovered.

The rate of skin reactions due to carbamazepine has been reported as ranging from 3% (17, 18) to 16.6% (19). Chadwick et al. (19) reported that eight of 48 patients receiving carbamazepine prophylactically for supratentorial craniotomy developed exanthematous skin eruptions. The authors suggested that this higher rate was due to loading doses administered to patients, which resulted in higher mean serum concentrations of carbamazepine. Simply reducing the dose may prove adequate to control the dermatologic manifestations in patients with less severe skin reactions (51). Vick (52) reported successfully treating three adults, who developed a carbamazepine-induced skin rash, with tapered doses of prednisone while the carbamazepine was continued. Others (53) have found that steroids may suppress the carbamazepine-associated drug rash but not necessarily other manifestations of carbamazepine hypersensitivity.

Exfoliative Dermatitis

Exfoliative dermatitis is characterized by widespread erythema with scaling due to exfoliation of the superficial skin. Constitutional symptoms are typically present, and occasionally a secondary infection develops. This dermatitis may appear abruptly in patients or, more usually, exfoliative dermatitis may be a progression of a benign, drug-induced skin eruption (21). Immediate withdrawal of the drug is indicated. Camarasa (54) reported the case of a 32-year-old man treated with carbamazepine who developed a generalized exfoliative dermatitis. The patient experienced prompt recurrence of the skin reaction upon resumption of carbamazepine treatment. The author confirmed the diagnosis with a positive patch test that used pure powder of 1% carbamazepine. Several other reports of exfoliative dermatitis secondary to carbamazepine treatment have been documented (55, 56). Exfoliative dermatitis has rarely been associated with imipramine and desipramine therapy (57).

Erythema Multiforme

Erythema multiforme is a cutaneous reaction pattern that is characterized by dull red macules, papules, vesicles, and pathognomonic target lesions (20) which are variable in size, configuration, and appearance. The typical eruption is acute, polymorphous, and sharply circumscribed, with a symmetrical distribution on the dorsal surface of the extremities (21). A fulminant, primarily bullous form of the disease that involves the mucosal surfaces including the eyes, mouth, and genital tract is frequently referred to as the Stevens-Johnson syndrome. The underlying mechanism of this syndrome remains unclear. It has been suggested that the lesions in erythema multiforme resemble chronic urticaria and that the pathogenesis of the reaction is mediated by IgE or is perhaps an immune-complex-mediated inflammation (2). Mianserin, a pyrazinoazepine compound (58), has been used as an antidepressant in Europe for approximately a decade. Several reports (59, 60) have documented mianserin as the cause of erythema multiforme, and one paper (15) mentioned fluoxetine as an etiologic agent. Carbamazepine has been reported (61, 62) to elicit the more severe Stevens-Johnson syndrome.

Fixed Drug Eruptions

Fixed drug eruptions are sharply delineated round or oval erythematous lesions that may have vesicles. These lesions, which occasionally are pruritic, recur at the same site each time the drug is ingested. Usually, the 2- to 3-inch circular lesion appears within a few hours to 24 hours after ingestion of the drug (63). The lesions usually subside 2 to 3 weeks after discontinuation of the offending agent, leaving residual hyperpigmentation (21). A case report of a fixed drug eruption due to carbamazepine has been documented (64); identical lesions recurred at identical sites after the reintroduction of carbamazepine.

Photosensitivity

Photosensitivity reactions, which are produced by an interaction of a drug with light energy (2), are limited to light-exposed areas such as the face, neck, back of hands, and arms. There are two mechanisms for photosensitivity: phototoxic and photoallergic. Acute phototoxic reactions are more common and develop promptly after initiation of drug treatment with exposure to ultraviolet light. These resemble a severe sunburn characterized by erythema and edema, followed by hyperpigmentation and desquamation (65). The reaction resolves when the drug is withheld. Photoallergic reactions involve immunologic mechanisms. DeSwarte (21) and Kaplan (2) speculated that radiant energy alters the drug to form a hapten, allowing complex formation with a cutaneous protein. This conjugate forms an antigen that precipitates an immunologic response. The rash is usually eczematous but can be lichenoid, urticarial, bullous, or purpuric (63). Phototoxic and photoallergic mechanisms are not always clinically distinct, and occasionally photosensitivity rash may result from both mechanisms.

All of the tricyclics, maprotiline, and carbamazepine are mentioned in *The Physicians' Desk Reference* as agents that may cause photosensitive reactions. While most photosensitivity reactions are benign and self-limited, a case has been reported (66) of a 38-year-old woman who developed a severe and prolonged photosensitivity eruption related to therapy with imipramine. Of note, 2 years before this reaction, the patient had developed a rash after treatment with doxepin. Kochevar (67) examined the phototoxicity response associated with protriptyline. She found that the photochemical products of protriptyline are capable of lysing red blood cells and eliciting erythematous papules on guinea pig skin.

Other

Toxic epidermal necrolysis is a potentially life-threatening condition that may represent a fatal variant of erythema multiforme (2, 68). In this condition, there is rapid development of a generalized erythematous rash that progresses to large, confluent bulla. The full thickness of epidermis then begins to desquamate, leaving exposed raw dermis. Death may result from fluid imbalance and secondary infection with sepsis. Although antidepressants rarely cause this condition, those implicated by case report include amoxapine (69), mianserin (70), and carbamazepine (68).

Acne-like lesions have been reported coincident with the initiation of maprotiline therapy (71). The lesions reappeared after the drug was readministered, which suggests an allergic drug reaction. Because of this finding, prudence is suggested in prescribing maprotiline to patients with facial acne.

Leukocytoclastic vasculitis, a disorder characterized by inflammation and destruction of the cutaneous small blood vessels, typically in the lower extremities, has been precipitated by trazodone (72). The case of leukocytoclastic vasculitis in a 61-year-old man with manic-depressive illness was documented with a biopsy and with the reemergence of the rash upon rechallenge with trazodone.

DIAGNOSIS

Cutaneous reactions to antidepressants are diagnosed primarily on the basis of the patient's history. The evidence is typically circumstantial. If the antidepressant was initiated within the week before the eruption, the evidence weighs more heavily toward that drug as the culprit. It is very unusual for a medication to which the patient has been continuously exposed to cause any cutaneous side effects (20). The evidence points more strongly toward an allergic reaction to antidepressants if the reaction occurs after a latent period, usually several days to 2 weeks, during which no ill effects were observed. Then, after a hiatus, if the patient who has become sensitized is given even small doses of the antidepressant, the second eruption is immediate (21, 23). In addition, if the patient demonstrates cross-reactivity to antidepressants in the same or a structurally similar class, the diagnosis of an allergic drug reaction is further supported (20).

RECOMMENDATIONS AND TREATMENT

If a cutaneous eruption occurs, especially during outpatient antidepressant treatment, it is advisable to discontinue that particular antidepressant and to substitute a medication from one of the other classes of antidepressants (see appendix 1). Salem et al. (73) successfully substituted doxepin for desipramine and imipramine for amitriptyline in two patients who initially developed dermatological problems with antidepressant therapy. Because of the high prevalence of rash with the tetracyclic maprotiline, it should probably not be used initially as an alternative. In a psychiatric inpatient setting, one could cautiously continue the presumed offending antidepressant. Because the diagnosis of drug-induced cutaneous eruption is often tentative and the exanthema is likely to be benign, the physician treating a patient with an affective illness must weigh these potential problems against the possibility of relapse of the depression should the medication be discontinued. In many instances, the patient may tolerate the rash with symptomatic treatment while continuing the antidepressant.

Once the antidepressant has been discontinued because of a cutaneous eruption, the physician should attempt to wait a period of time before administering an alternative class of antidepressants. One week is an adequate period to assess improvement of the rash, once the offending antidepressant has been discontinued. The alternative antidepressant can then be administered.

A psychiatrist prescribes carbamazepine only for patients with an affective disorder that is resistant to traditional treatments. Adverse dermatological manifestations may be avoided by slowly increasing the dose to the maintenance level (19). Carbamazepine requires the practitioner to monitor blood counts and liver function tests (74). In addition, it has not yet been approved by the Food and Drug Administration for treatment of affective illness. Thus, if a rash occurs, it is recommended that the clinician discontinue the drug.

Most rashes that are mild reactions clear within several days after the drug has been discontinued and require no additional treatment. Antihistamines may be prescribed to relieve pruritus. If the patient is anxious, hydroxyzine hydrocloride may be beneficial. Treatment of more severe skin reactions depends on the nature of the eruption and requires the consultation of a dermatologist. Glucocorticoid therapy is begun if the process becomes significantly worse after the antidepressant has been discontinued. Generally, after a photosensitivity reaction, the patient should be advised to continue to avoid sunlight and to use topical sunscreens (21) with maximum sunburn protection. In addition, if a patient with asthma and aspirin sensitivity develops an adverse cutaneous reaction, the clinician should consider the possibility of a sensitivity to tartrazine and switch to another antidepressant that does not contain yellow number 5.

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APPENDIX 1. Selected Antidepressant Drugs Used in the United States

- Tricyclic Antidepressants
  - Dibenzocycloheptene: amitriptyline, nortriptyline, protriptyline
  - Dibenzazepine: imipramine, desipramine, trimipramine
  - Dibenzoxepin: doxepin
  - Dibenzoxazepine: amoxapine
- Tetracyclic Antidepressants
  - Dibenzobicyclooctadiene: maprotiline
- Monoamine Oxidase Inhibitors
  - Hydrazine: phenelzine, isocarboxazid
  - Nonhydrazine: tranylcypromine, pargyline
- Other
  - Triazolopyridine: trazodone
  - Benzodiazepine: alprazolam
  - Iminostilbene: carbamazepine

APPENDIX 2. Cutaneous Manifestations Caused by Antidepressant Drugs (material taken in part from references 21 and 29)

- Dermatitis medicamentosa
  - Pruritus: amoxapine, maprotiline, tricyclic antidepressants
  - Urticaria: carbamazepine, trazodone, tricyclic antidepressants, maprotiline
  - Exanthematous eruptions (morbilliform or maculopapular): carbamazepine, maprotiline, tricyclic antidepressants, trazodone, fluoxetine, alprazolam
  - Exfoliative dermatitis: carbamazepine, tricyclic antidepressants
  - Erythema multiforme-like eruptions: carbamazepine, mianserin, fluoxetine
    - Stevens-Johnson syndrome: carbamazepine
  - Erythema nodosum-like eruptions
  - Fixed drug eruptions: carbamazepine
  - Purpuric eruptions: carbamazepine, imipramine
  - Photosensitivity: maprotiline, carbamazepine, tricyclic antidepressants
- Other drug-induced dermatoses (possibly allergic)
  - Vesiculobullous eruptions: carbamazepine
  - Toxic epidermal necrolysis: amoxapine, carbamazepine, mianserin
  - Vasculitis: amoxapine, trazodone
  - Lichen planus-like eruptions: carbamazepine
- Other drug-induced dermatoses (not allergic)
  - Acneiform eruptions: tricyclic antidepressants, maprotiline
  - Pigmentary changes: amitriptyline, imipramine
  - Alopecia: carbamazepine, trazodone

Controlled Study of Verapamil for Treatment of Panic Disorder

Ehud Klein, M.D., and Thomas W. Uhde, M.D.

The authors conducted a 16-week double-blind, crossover study in 11 patients with panic disorder to study the effects of verapamil, a calcium channel blocker commonly used in the treatment of cardiovascular disorders, on the treatment of panic disorder. Their findings suggest that verapamil has modest antianxiety and antipanic properties.

(Am J Psychiatry 1988; 145:431–434)

Calcium channel blockers have gained wide use over the last several years in the treatment of cardiovascular disorders (1, 2). The most commonly used drugs in this class are verapamil and nifedipine. These drugs share the ability to block depolarization-induced calcium influxes into cells (2). The abundance of calcium in body tissues and its central role in a variety of neurobiological processes, such as neurotransmitter release, postsynaptic effects, electrical activation of excitable cells, and hormone release (3–8), make neural tissue a potentially important target for these drugs. In addition to these actions, several other lines of evidence suggest that calcium channel blockers might have therapeutic effects in the treatment of anxiety disorders. For example, experimental data suggest that the clinical manifestations of anxiety in general and panic attacks in particular may be in part associated with noradrenergic overactivity (7, 9–11), especially that originating from the locus ceruleus, which contains an estimated 50% of brain norepinephrine (12). Calcium blockers, especially verapamil, have been shown in vitro to inhibit norepinephrine release from brain synaptosomal preparations (13, 14). Calcium channel blockers also increase cerebral blood flow (15), and reductions in cerebral blood flow or brain hypoxia have been hypothesized in anxiety states (16; Uhde et al., unpublished paper, 1987). Cardiovascular manifestations of anxiety, namely, tachycardia, palpitations, and increased blood pressure, might improve with verapamil therapy since calcium blockers have negative chronotropic and inotropic effects (1, 2).

Reports on the efficacy of calcium channel blockers in the treatment of anxiety disorders have so far been anecdotal. A recent study (17) in which four of seven patients with panic disorder had a favorable response to an open trial of 240 mg/day of verapamil suggested that verapamil treatment might reduce pathological anxiety and block panic attacks. The aforementioned preclinical evidence and the good safety record of these drugs in the treatment of cardiovascular disease prompted us to evaluate the efficacy of verapamil in the treatment of panic disorder.

METHOD

Patients referred to our outpatient clinic were interviewed by a staff psychiatrist (E.K.) and included in the treatment program if they satisfied Research Diagnostic Criteria (RDC) (18) for panic disorder. Initial evaluation included a detailed interview and mental status examination, physical and neurological examination, chest X-ray, ECG, EEG, CAT scan, and routine blood tests.

Fourteen panic disorder patients, 10 women and four men (mean ± SD age, 35.6 ± 7.0 years; range, 26–49 years), participated in this study. Twelve patients

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(86%) also met RDC for phobic disorder (agoraphobia subtype) while only one patient (7%) had sufficient depressive symptoms to meet concomitant *DSM-III* criteria for major depressive disorder. Their mean ± SD duration of illness from onset of the first panic attack was 10.1 ± 5.6 years (range, 3–22 years). Their mean ± SD Spielberger state anxiety and Beck Depression Inventory ratings, obtained before the study began, were 56.6 ± 9.0 (range, 35.4–78.0) and 9.2 ± 6.5 (range, 1.0–30.0), respectively. Lifetime exposure to psychotropic medications was carefully assessed in each patient. Ten (71%) of the 14 patients had previously been treated with medication: four had been exclusively treated with benzodiazepines (alprazolam or diazepam) alone, and six had been treated with both benzodiazepines and tricyclic or monoamine oxidase inhibitor antidepressants. In addition, two of the 10 patients had also been treated with clonidine, and one had been treated with lithium. Seven (70%) of these 10 patients described moderate to good therapeutic responses to one of the medications.

The study was designed as a double-blind, crossover study, and each patient received both verapamil and placebo. The drug trial began after all patients gave informed consent.

If patients were receiving medications at the time of entry into the study, the medications were discontinued and the patients underwent a washout period during which placebo was administered blindly for at least 3 weeks. Then, each patient received 4 weeks of placebo treatment. After this first placebo period, verapamil was given at a dose of 160 mg/day and increased by 160 mg/day at weekly intervals to a maximum dose of 480 mg/day, which was maintained for 5 weeks. The dose was then decreased to 240 mg/day for 1 week before discontinuation of verapamil and placebo substitution for an additional 4 weeks. Thus, the study was an off-on-off design lasting a total of 16 weeks. During the dose increases and once after the maximum dose was achieved, ECG monitoring was performed to rule out the development of significant first-degree atrioventricular block.

Patients were evaluated and rated weekly by a nurse who was blind to the research design and the treatment status of the patient. A psychiatrist (E.K.) made weekly clinical assessments and medication adjustments. Medications were administered in pink opaque capsules and given in divided doses. Blood pressure and pulse rates were obtained weekly. The state portion of the Spielberger State-Trait Anxiety Inventory (19), the Zung Self-Rating Anxiety Scale (20), the Beck Depression Inventory (21), and an unpublished NIMH panic attack inventory were administered weekly. Anxiety attacks were categorized as full-blown panic attacks or as limited symptom attacks according to *DSM-III-R* criteria. Agoraphobia was also rated weekly on an NIMH 15-point scale, with 1 indicating no impairment and 15 indicating a state of being totally homebound.

Analysis of variance (ANOVA) with repeated measures comparing pretreatment placebo period, treatment period, and posttreatment placebo period was used with the corrected Huynhfeldt probability; post hoc analyses were performed with the Tukey test. The relationship between several different clinical and physiological measures was assessed with Pearson correlation coefficients. For the purposes of statistical analysis and graphic representation, limited symptom and full panic attacks were assigned a relative value of one-half and one panic attack, respectively. The Wilcoxon signed rank test was then used for comparison of the number of panic attacks before and during treatment. All data are reported as mean ± SD.

RESULTS

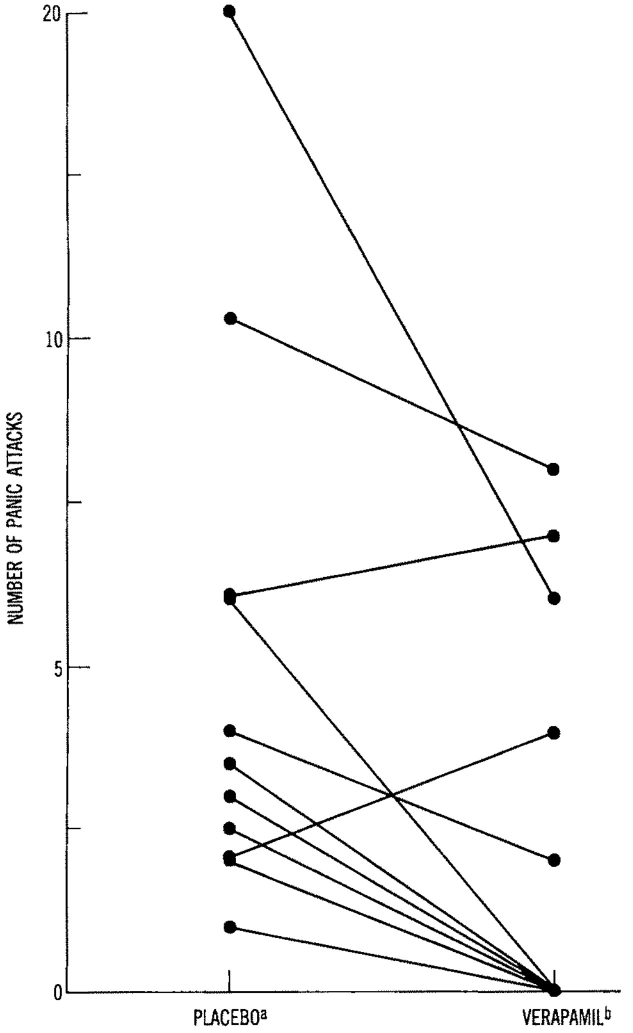
Of the 14 patients who entered the study, three either dropped out or were withdrawn, leaving 11 patients who completed the study. One dropout, who was severely disabled with multiple panic attacks and depression (the patient who met *DSM-III* criteria for major depressive disorder) before entering the study, was switched for ethical reasons to open treatment with alprazolam and imipramine after she developed suicidal ideation; two other patients dropped out because they later found it unacceptable to receive blindly administered medications.

The ANOVA (first placebo versus active drug versus second placebo periods) revealed a significant drug effect on anxiety as measured by the Zung anxiety scale (mean ± SD ratings: 58.0 ± 10.5, 51.9 ± 11.1, 51.5 ± 10.6, respectively; $F=4.19$, $df=1.6, 16.1$, $p<0.04$). Post hoc analysis revealed a significant difference between Zung ratings during the pretreatment placebo period and the posttreatment placebo period ($p<0.05$) and a similar trend in the difference between the pretreatment and the treatment values ($p<0.06$); however, there were no significant changes on the Spielberger state anxiety, the NIMH agoraphobia, and the Beck depression scales. Nine (82%) of 11 patients had significantly fewer panic attacks during the last 4 weeks of verapamil treatment than during the 4 weeks of placebo preceding verapamil ($T=6.0$, $N=11$, $p<0.02$) (figure 1).

As expected, there was a significant reduction in diastolic blood pressures (mean reduction: 6.8 mm Hg; $F=7.5$, $df=2, 20$, $p<0.004$) and mean arterial blood pressures ($F=5.45$, $df=2, 20$, $p<0.01$).

There was a correlation between baseline (i.e., after 4 weeks of placebo before verapamil treatment) ratings on the Zung anxiety and Beck depression scales ($r=0.9$, $df=9$, $p<0.001$). Although no significant correlation was found between baseline Zung anxiety ratings and the Zung change scores during treatment, there was a trend for a significant correlation between the baseline ratings on the Beck depression scale and the decrease in Zung anxiety scores with treatment ($r=0.57$, $df=9$, $p<0.07$). A significant positive correlation also was found between Zung anxiety ratings at

FIGURE 1. Frequency of Panic Attacks During Last 4 Weeks of Verapamil Treatment and Last 4 Weeks of Placebo Before Verapamil Treatment in 11 Patients With Panic Disorder



[a]Four weeks before verapamil.
[b]Last 4 weeks at a dose of 480 mg/day.

baseline before verapamil treatment and diastolic blood pressure during ($r=0.67$, df=9, $p<0.02$) and after ($r=0.75$, df=9, $p<0.008$) verapamil treatment.

No significant cardiovascular side effects were observed in any of the patients. The decrease in blood pressure was not associated with any subjective complaints, and ECG monitoring did not reveal a clinically significant (>0.24 msec) increase in P-R intervals. One patient complained of severe constipation, which resolved soon after drug withdrawal.

DISCUSSION

Our findings provide preliminary evidence for the anxiolytic and antipanic effects of verapamil. A statistically significant, although clinically modest, reduction in the number of panic attacks and the Zung anxiety ratings was observed along with the expected hypotensive effect of this drug. There was no significant change in state anxiety as reflected by the Spielberger anxiety scale. Despite a significant decrease in the number of panic attacks, there was no significant improvement in agoraphobia over the relatively brief time course of this study. In future studies, it will be important to determine whether a clinically impressive reduction in avoidance behaviors can be achieved with longer term administration.

The greater change on the Zung than on the Spielberger anxiety scale is consistent with our previous drug treatment and challenge studies. The greater change in Zung anxiety ratings may also reflect more robust improvement in somatic symptoms than in psychic dimensions of anxiety. The lack of change on the Beck depression scale was not unexpected since none of the patients who completed the study had clinically significant degrees of depression at baseline or developed clinical symptoms of depression during the study period. The decrease in the number of panic attacks was statistically significant, but the overall clinical effects on the blockade of panic attack appeared modest.

The significant positive correlation between pretreatment Zung anxiety ratings and diastolic blood pressure measurements throughout the study indicates that a higher degree of initial anxiety tended to be associated with higher blood pressure throughout the study. No significant correlation was observed, however, between the changes in the Zung ratings and changes in blood pressure during treatment.

There was a trend toward higher ratings of anxiety in the last 2 weeks than in the first 2 weeks of the second placebo phase. This trend, although not statistically significant, suggests a positive drug effect that lasted into the first 2 weeks after discontinuation of drug treatment. This pattern also suggests that there were no withdrawal symptoms despite the rapid discontinuation of the drug, since such symptoms would have been expected within the first 2 weeks after drug withdrawal.

From a clinical perspective, four patients rated themselves as having markedly benefited from the drug, three had a marginal response, and four were complete nonresponders. Two of the patients, one responder and one nonresponder, were given verapamil a second time according to the same schedule and showed a similar response pattern. The patient who responded to the two verapamil trials was then discharged with a recommendation to continue verapamil treatment; she continued the drug for several months and 1 year after discharge is receiving no medications and maintaining a good remission of her symptoms.

Possible mechanisms of action of verapamil include diminution of autonomic and cardiac function, reduction in cerebral blood flow, or inhibition of noradrenaline release. That verapamil's modest anxiolytic action is mediated by means of the first two mechanisms seems unlikely since nifedipine, which we have found ineffective in the treatment of phobic anxiety, has effects similar to verapamil on cardiac and brain vascular systems. On the other hand, verapamil has been shown to be more potent than nifedipine in inhibiting noradrenaline release from synaptic vesicles (13, 14), a finding that could explain the difference between the effects of the two drugs on anxiety states.

Calcium blockers have been shown to be a heterogenous group of drugs that share the ability to block slow voltage-dependent calcium currents but differ in many other respects (22). Two groups of calcium channel blockers are known: verapamil and related compounds (diltiazem and prenylamine) and dihydropyridine calcium blockers (nifedipine, nitrendipine, and nimodipine). The two groups bind to different sites on the calcium channel (23) and vary in their ability to block neurotransmitter release from presynaptic vesicles (13, 14).

Our study suggests that verapamil has modest anxiolytic and antipanic effects. Additional studies are required to substantiate this finding and compare the efficacy of verapamil to drugs, such as imipramine, phenelzine, and alprazolam, that have a well-established role in the treatment of panic disorder.

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Personality Pathology in Recurrent Depression: Nature, Prevalence, and Relationship to Treatment Response

Paul A. Pilkonis, Ph.D., and Ellen Frank, Ph.D.

Personality assessments of 119 treatment-responsive patients with recurrent unipolar depression revealed that nearly half of the patients (48%) showed some personality disturbance. The most common personality features were avoidant (30.4%), compulsive (18.6%), and dependent (15.7%). Factor analyses of personality data in this homogeneous population yielded results that were consistent with previous factor analytic studies of personality features and clinical descriptions of depressed patients. Most notably, a discriminant function analysis using personality variables alone was able to distinguish (with 65% accuracy) between patients who responded normally to treatment and those who responded more slowly.

(Am J Psychiatry 1988; 145:435–441)

The inclusion of axis II for personality disorders in *DSM-III* has heightened awareness of potential interactions between major psychiatric syndromes and longstanding personality features (1, 2). In the area of affective disorders, publications (3, 4) from the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression have examined the topic of personality and depression specifically and have addressed some of the conceptual problems it raises (e.g., the "state-trait" issue). Historically, the relationship between personality attributes and vulnerability to depression has attracted considerable attention. Early clinical contributions included the work of Freud (5), Abraham (6), Rado (7), and Klein (8). More recent reviews of the research literature have been provided by Akiskal et al. (9), Chodoff (10), and von Zerssen (11).

The purposes of the present study were to identify the most common personality traits and disorders in a homogeneous sample of patients with recurrent unipolar depression and to determine the results of factor analyses of both a clinician-rated measure of personality disorder dimensions and a self-report measure of personality traits. We also examined the convergent validity between these two perspectives and domains (i.e., clinician's report versus self-report, personality disorders versus personality traits) and their ability to predict rate of treatment response, a measure of predictive validity.

METHOD

Study Design

After giving informed consent, patients between the ages of 21 and 65 who suffered from a current major depression, confirmed by interview with the Schedule for Affective Disorders and Schizophrenia (SADS) (12), were entered into the Maintenance Therapies in Recurrent Depression protocol if the index episode was at least their third lifetime episode of major, unipolar depression. It was also necessary that the immediately preceding episode occurred no more than 2½ years before the onset of the current one and that previous episodes required treatment or resulted in significant functional impairment. In addition, the patient was required to have minimum scores of 15 on the Hamilton Rating Scale for Depression and 7 on the Raskin Severity of Depression Scale. Patients with primary diagnoses other than unipolar depression (e.g., alcoholism, phobic disorder, or panic disorder) were excluded, as were those who met *DSM-III* criteria for borderline or antisocial personality disorder. This last exclusion obviously limits to some extent the range of traits and disorders to be found in our sample.

After a 2-week drug-free period, severity of depression was reevaluated and patients who remained symptomatic were given a complete initial assessment including biological (all-night sleep EEG and neuroendocrine studies) and psychosocial (e.g., social adjustment and social support) measures. Because of the probable influence of acute illness on personality instruments (3), however, *personality was not evaluated at this time.*

All patients then received the same acute treatment regimen: imipramine (150–300 mg/day) and interpersonal psychotherapy (13), offered weekly for 12

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TABLE 1. Demographic and Clinical Characteristics of 119 Patients With Major Depression

Variable	Mean	SD
Age (years)	39.8	10.6
Age at onset of first episode (years)	26.8	9.9
Number of previous episodes	5.4[a]	3.0
Duration of current episode (weeks)	23.3	18.3
Baseline Hamilton depression score	21.9	4.7

[a]Values of 11 or more, accounting for 15% of the sample, were truncated to a score of 11 because of the skewedness of the original distribution.

weeks, biweekly for 8 weeks, and monthly thereafter. At the point when patients had maintained a Hamilton score of 7 or less and a Raskin score of 5 or less for 3 weeks, a second biological and psychosocial evaluation was completed. At this (continuation treatment) evaluation, personality was assessed for the first time using both self-report and interview measures (described later in Method). Patients remained in continuation treatment for an additional 17 weeks, during which both Hamilton and Raskin scores and imipramine dose were required to remain stable. A third (premaintenance) evaluation was then conducted, after which patients were randomly assigned to one of five maintenance treatments for 3 years or until they experienced a recurrence of illness. The five maintenance treatments consisted of interpersonal psychotherapy—alone, with placebo, or with imipramine—and imipramine or placebo given at a medication clinic. Patients were evaluated every 3 months.

Patients

Data for the present report came from the first 119 patients entered into the protocol who were able to 1) complete at least 16 weeks of acute treatment, 2) achieve a clinical remission, 3) remain asymptomatic during the 20-week period of continuation treatment, and 4) be assigned to maintenance therapy. Eighty-nine (75%) of the patients were women and 30 were men; 69 (58%) were diagnosed as having definite, endogenous depression according to Research Diagnostic Criteria. Other demographic and clinical characteristics are presented in table 1.

On the average, the patients were middle-aged individuals who had relatively early onsets of illness. Many patients had experienced more than the two required previous episodes of major, unipolar depression; however, as required by the entry criteria, none had experienced an episode of mania. The group was severely ill, with scores on the Hamilton Rating Scale for Depression that were more characteristic of inpatients than outpatients, and had, on average, been ill for almost 6 months at the time of initial assessment.

The 119 patients represented over half (52%) of the 230 patients accepted into the Maintenance Therapies in Recurrent Depression protocol. Of the original group of 230, only 17 patients dropped out or were terminated for noncompliance before or during acute treatment; however, 25 were unable to remain in treatment for other reasons (e.g., intolerable side effects, need for hospitalization, previously undetected medical problems). Another 32 patients failed to achieve a clinical remission. During continuation treatment, 25 patients were lost: 13 because of an inability to sustain a stable remission, four because of patient noncompliance, five for miscellaneous "other" reasons, and three because of the appearance of side effects. Twelve patients were progressing through continuation treatment at the time of our analyses and were not included in the present sample.

For the purposes of the present investigation, we categorized the 119 treatment responders assigned to maintenance according to rate of response to acute treatment, using the algorithm described by Frank et al. (14). Sixty-one of the patients showed a complete remission within 8 weeks and remained well thereafter ("normal responders"); 43 patients showed a more variable response but achieved remission by 16 weeks ("slow responders"); and 15 patients, although classified at 16 weeks as only partially responsive to the combined treatment regimen, were ultimately able to achieve remission and enter continuation ("partial responders"). Because of the limited size of the third subgroup, a decision was made to consider them as "very slow responders" and thus to combine the slow and partial responder categories for the current analysis.

Personality Measures

Personality data were collected at two assessments, the continuation and premaintenance evaluations. The results reported here come only from the premaintenance evaluations to ensure that personality ratings were not confounded by varying levels of depressive symptoms. We mentioned previously our concern with such confounding at the time of intake, and we continued to regard it as an important issue at the beginning of the continuation period, when patients had been well for only a short period of time (3 weeks) and varied somewhat in the absolute level of symptomatic remission that they had attained. At the premaintenance evaluation, however, all patients had been asymptomatic for a period of at least 20 weeks and no differences were observed between the two groups on Hamilton or Raskin scores, which gave us greater confidence in the validity of the personality data.

Self-report. The Hirschfeld-Klerman Personality Battery was developed for use in the NIMH Collaborative Program on the Psychobiology of Depression. It consists of 436 self-report items that were taken from 17 scales drawn from five previously established measures of personality (see appendix 1). Patients were asked to complete the battery during the 3 nights they spent in the sleep laboratory for each evaluation.

Ratings by clinicians. The Personality Assessment

Form requires 6-point, dimensional ratings for each of the 11 personality disorder categories included in *DSM-III*. It was developed by the NIMH Treatment of Depression Collaborative Research Program in an attempt to examine personality disorder as a potentially important variable that moderates treatment response among patients with affective disorders (2, 15). In the present study, the Personality Assessment Form was completed by the patient's primary clinician (a psychiatric social worker or clinical psychologist) after an interview involving a series of 15 to 25 probe questions for each of the *DSM-III* personality disorders. In making their ratings, clinicians were also expected to use the data obtained over the course of their face-to-face interactions with patients in psychotherapy. The use of this personality form was instituted approximately 6 months after the current protocol had begun. Therefore, these ratings were available only for a subsample of 102 patients (51 normal responders, 36 slow responders, and 15 partial responders).

Data Analysis

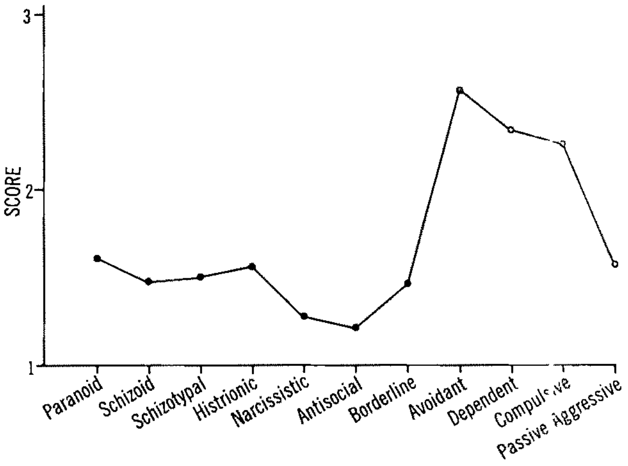
Two factors analyses were performed: the first was done with the 11 ratings from the Personality Assessment Form (on a sample of 102 patients), and the second was done with the 17 scale scores from the Hirschfeld-Klerman Personality Battery (on a sample of 119 patients). The factor analysis program from the Statistical Package for the Social Sciences (16) was used. The "simplest" technique (in the sense of requiring the fewest assumptions) was applied to the data, that is, principal components analysis with orthogonal rotation.

RESULTS

Prevalence of Personality Disorders

The prevalence of personality disorders was substantial within the sample. Using a score of 4 or more on the 6-point scale of the Personality Assessment Form, we rated 49 of 102 patients (48%) as having some personality disturbance. The most common personality disorders were avoidant (30.4%), compulsive (18.6%), and dependent (15.7%); some patients had more than one rating above the threshold. When clustered into the three larger groups that the *DSM-III* nosology hypothesizes, the majority of patients with personality disorders fell into cluster 3, the "fearful, anxious" group. Forty-five of the 49 patients had ratings of 4 or more on the cluster 3 dimensions; 13 of these patients also had ratings of 4 or more in cluster 1 or 2; this left 32 patients (of 49, or 65%) with pure cluster 3 disorders. Figure 1 displays the mean profile for the sample across all ratings on the Personality Assessment Form. It is important to note that the base rates for several of the disorders in clusters 1 and 2 were low, since this fact influences the kinds of factors that could be expected to emerge.

FIGURE 1. Mean Personality Assessment Form Scores of 102 Patients With Major Depression



Personality Factors

The Personality Assessment Form ratings of personality disorder and the scale scores of personality traits from the Hirschfeld-Klerman Personality Battery were factor analyzed in order to explore the underlying structure among these variables. Since the Personality Assessment Form included only 11 variables (personality disorder dimensions), we expected a factor solution in which no more than two or three factors could be interpreted. In fact, three factors (with eigenvalues greater than 1) were extracted. The standardized factor coefficients for each variable are summarized in table 2.

The three factors accounted for 62.4% of the variance in the Personality Assessment Form ratings. The first factor included all the dimensions from cluster 2 of *DSM-III* (the "dramatic, expressive" personalities), but it also contained a significant loading for passive-aggressive personality. The additional factors differentiated two subgroups within cluster 3 (the "fearful, anxious" personalities). The second factor contained high loadings for dependent and avoidant features, with a significant but lesser weighting for paranoid personality. This factor appeared to capture the "anxious attachment" characteristic of shy, dependent, and inhibited persons. The loading for paranoid features is probably best interpreted as a measure of interpersonal sensitivity, rather than as an indication of frank paranoia (especially in this sample of affective patients). The third factor represented a measure of compulsive personality, with additional significant loadings on the schizoid and schizotypal dimensions. This factor reflected a rather asocial, inward-directed orientation.

The factor analysis of the 17 scales included in the Hirschfeld-Klerman battery produced a solution with

TABLE 2. Standardized Factor Coefficients for the Personality Assessment Form Scores of 102 Patients With Major Depression

Personality Disorder	Standardized Factor Coefficient[a]		
	Factor 1	Factor 2	Factor 3
Paranoid	0.39	0.61	0.32
Schizoid	0.17	−0.15	0.82
Schizotypal	0.28	0.25	0.69
Histrionic	0.68	0.36	0.15
Narcissistic	0.71	0.14	0.28
Antisocial	0.76	0.08	0.02
Borderline	0.68	0.38	0.14
Avoidant	0.37	0.75	0.10
Dependent	0.02	0.87	0.06
Compulsive	0.02	0.27	0.61
Passive-aggressive	0.71	0.20	0.08

[a]Factors 1, 2, and 3 accounted for 39.9%, 11.4%, and 11.1% of the variance, respectively. Loadings greater than 0.40 are underlined.

TABLE 3. Standardized Factor Coefficients for the Hirschfeld-Klerman Personality Battery Scores of 119 Patients With Major Depression

Personality Scale	Standardized Factor Coefficient[a]			
	Factor 1	Factor 2	Factor 3	Factor 4
General activity	0.14	0.80	−0.06	0.14
Restraint	0.04	−0.31	−0.13	0.78
Ascendance	0.51	0.51	0.47	0.02
Sociability	0.44	0.73	0.07	−0.26
Emotional stability	0.75	0.38	−0.30	0.05
Objectivity	0.81	0.14	−0.24	0.05
Thoughtfulness	−0.16	−0.26	0.55	0.50
Emotional reliance on another person	−0.87	0.09	0.03	0.13
Lack of social self-confidence	−0.80	−0.36	−0.25	−0.11
Assertion of autonomy	−0.11	0.01	0.03	0.47
Obsessionality	0.29	0.23	−0.10	0.71
Hysteria	−0.36	0.20	0.67	0.08
Orality	−0.84	−0.28	−0.07	−0.05
Neuroticism	−0.79	−0.28	0.32	0.05
Extraversion	0.41	0.72	0.17	−0.36
Ego control	0.03	−0.01	−0.80	0.30
Ego resilience	0.78	0.30	−0.24	−0.09

[a]Factors 1, 2, 3, and 4 accounted for 40.4%, 14.4%, 10.6%, and 6.4% of the variance, respectively. Loadings greater than 0.40 are underlined.

four factors. Table 3 summarizes the factor matrix that resulted from the self-report measures. These four factors accounted for 71.8% of the variance in the ratings. The first factor (with significant loadings for 10 of the 17 scales), which is best interpreted as a measure of adaptive personality functioning, indicated ego resilience, social self-confidence, emotional stability, self-reliance, and a lack of neuroticism (to cite several of the highest loadings on this factor). The second factor, a measure of extraversion, had significant loadings for extraversion and the scales reflecting activity level, sociability, and ascendance. The third factor, which appeared to be a measure of histrionic personality, had the highest loadings for hysterical features and lack of ego control. The last factor reflected a dimension of obsessive-compulsive features and had significant loadings for restraint, obsessionality, thoughtfulness, and autonomy. This factor structure is consistent with previous factor-analytic studies of personality traits, since it includes primary factors for neuroticism (or in this case the converse, ego resilience) and extraversion. The third and fourth factors for histrionic and obsessional features may be more specific to our depressed sample, but even they are not dissimilar to factors for impulsivity and conscientiousness that appear in the frequently replicated "five-factor model" of personality (16–18).

Convergent Validity

In terms of face validity, factors 2 and 3 from the Hirschfeld-Klerman battery (extraversion and histrionic features) seem to have some of the same aspects as factor 1 from the Personality Assessment Form ratings ("dramatic, expressive" dimensions). In addition, factor 4 from the Hirschfeld-Klerman battery (obsessionality) appears to be similar to factor 3 from the Personality Assessment Form ratings (compulsive personality). To examine further the convergent validity between ratings of traits and disorders, two techniques were used. First, factor scores on each of the seven factors were computed for all patients, and the correlations among them were inspected. The largest correlation—$r=-0.41$, $df=101$, $p<0.001$—appeared as a negative relationship between factor 2 from the Hirschfeld-Klerman battery (extraversion) and factor 3 from the Personality Assessment Form (compulsive personality). Hirschfeld-Klerman factor 1 (ego resilience) and Personality Assessment Form factor 2 (avoidant/dependent features) were also significantly and negatively correlated—$r=-0.36$, $df=101$, $p<0.001$. Although shy, dependent people may not be more "neurotic" (in absolute terms) than compulsive or dramatic people, it appears that they were willing to portray themselves in this way, which resulted in a negative correlation between clinical judgments of avoidant and dependent features and self-reports of ego resilience. Finally, the expected positive correlation between Hirschfeld-Klerman factor 3 (histrionic features) and Personality Assessment Form factor 1 (dramatic, expressive personality) did appear—$r=0.27$, $df=101$, $p<0.01$.

Second, patients were divided into those judged to have a personality disorder (i.e., any rating on the Personality Assessment Form of 4 or more) and those without such a rating. Using the presence versus absence of a personality disorder as the independent variable, we computed t tests with each of the Hirschfeld-Klerman trait scales as dependent variables. Significant differences were found on 10 of the 17 scales ($p<0.05$). The strongest effects ($p<0.001$) occurred on the scales for neuroticism, ego resilience, orality, sociability, and objectivity. In all cases, patients judged to have a personality disorder rated themselves as less functional or less normative on the trait measures. In general, then, the evidence for convergent validity between these two perspectives and domains (i.e., clinician-rated personality disorders and self-reported personality traits) is quite good.

Predictive Validity

Having identified seven personality factors (three from clinical judgments and four from self-reports), we were interested in their relationship to treatment response. As described earlier, all patients received combined treatment (imipramine and interpersonal psychotherapy) for their acute depressive episode. Using rate of response as the independent variable (contrasting normal versus slow or very slow response), we performed t tests with the seven factor scores as dependent variables. The tests were also done using the *DSM-III* cluster scores (summed from the relevant Personality Assessment Form dimensions) and the total score from the Personality Assessment Form (the sum of all 11 personality ratings, representing a general measure of personality disturbance) as dependent variables. In addition, a chi-square analysis was performed on the 2 × 2 frequency table that resulted when response (normal versus slow/partial) was crossed with the presence versus absence of any personality disorder (i.e., any rating of 4 or more on the Personality Assessment Form).

From these analyses, a number of significant results emerged. The strongest effects occurred with Hirschfeld-Klerman factor 1 (ego resilience) ($t=3.09$, $df=117$, $p<0.003$) and the dichotomy of presence versus absence of any personality disorder ($\chi^2=7.70$, $df=1$, $p<0.006$). As one would expect, normal responders rated themselves as having more ego resilience and were less likely to have received a personality disorder diagnosis (only 33% of normal responders, but 63% of the slow or partial responders, were given a Personality Assessment Form rating of 4 or more). In addition, normal responders had lower total scores on the Personality Assessment Form ($t=2.20$, $df=99$, $p<0.03$), an effect due especially to lower scores on *DSM-III* cluster 1; odd, eccentric features ($t=2.35$, $df=99$, $p<0.03$); and *DSM-III* cluster 3, fearful, anxious features ($t=1.99$, $df=99$, $p<0.05$).

In order to integrate these effects in a multivariate fashion, a discriminant function analysis was performed. The variables that had been found in univariate analyses to relate to treatment response were entered into a stepwise analysis aimed at minimizing Wilks' lambda. The analysis was revealing, although it should be regarded as exploratory since it may capitalize on opportunistic relationships among the predictors. The variables included in the analysis (with their standardized discriminant function coefficients in parentheses) were Hirschfeld-Klerman factor 1, ego resilience (.78) and the presence versus absence of any personality disorder (−.51, with presence coded 1 and absence coded 0). The canonical correlation between these predictors and treatment response was .39, and the discriminant function was able to correctly classify 64% of the normal responders and 66% of the slow/very slow responders (65% overall classification accuracy).

DISCUSSION

In answer to our original questions, it is clear that personality disorders were common in our sample of patients with recurrent depression, and the fearful, anxious personality disorder dimensions were most prevalent among patients who responded (even if slowly) to acute treatment of their index episodes. The factor structure that emerged from the self-report Hirschfeld-Klerman Personality Battery scales was consistent with that described in previous factor-analytic studies (17–19), in which dimensions of neuroticism and extraversion have been prominent. The factor structure that resulted from the Personality Assessment Form ratings was more novel and included three dimensions: factors for "dramatic, expressive" features; for compulsive, asocial personalities; and for dependent, avoidant, "anxiously attached" personalities. These last two factors (unlike the first one) do not correspond to the a priori clusters described in *DSM-III*, but they make good clinical sense and conform rather well with other descriptions of the personalities of depressed patients found in the literature.

Bowlby (20), for example, discussed both "compulsively self-reliant" and "anxiously attached" people and their predispositions toward depression. Compulsively self-reliant people disavow any interest in close, interpersonal relationships and are often scornful of others who directly express their needs for such ties. At the other extreme lie anxiously attached individuals who are eager for interpersonal contact but, at the same time, are inhibited from soliciting it. When they do finally establish relationships, such people frequently become excessively dependent on attachment figures. Bowlby regarded both excessive dependency and excessive autonomy as the results of frustrated attachment needs. Similar dichotomies have been described by other investigators. Beck (21) distinguished between "socially dependent" and "autonomous" depressed patients; Blatt et al. (22, 23) described "anaclitic" (dependent) and "introjective" (self-critical) depressed patients; and Arieti and Bemporad (24) have discussed the depressed patient's need for either a "dominant other" or a "dominant goal." The factors we derived from our clinicians' ratings of personality disorder dimensions provide suggestive, additional evidence for these two prototypes.

We would emphasize not only the structure of the factors that emerged, but also their relationship to treatment response. Factor 1, ego resilience, from the Hirschfeld-Klerman battery and the presence of any personality disorder on the Personality Assessment Form were significantly related to rate of treatment response. Taken together, these two measures allowed us to correctly classify 65% of our patients as either normal or slow/very slow treatment responders. We are impressed by the fact that approximately two out of three patients can be identified in this way by using only personality variables (given the range of demographic, clinical, and treatment variables that have been used in the research literature to predict prognosis).

The results for ego resilience are consistent with earlier work showing that measures of neuroticism tend to be associated with poorer outcomes among depressed patients (25, 26). This literature is difficult to interpret at times because of the state-trait problem (i.e., ratings of neuroticism vary in direct relation to depressive affect). It is important, however, to emphasize that in our sample these ratings and self-reports were not confounded with levels of depressive symptoms. At the point (premaintenance) that these data were gathered, all patients were asymptomatic and had been that way for an extended period of time (at least 20 weeks).

An additional qualification is necessary. Our sample was a select one for at least two reasons: the inclusion criteria for the protocol and the requirement that patients be sufficiently responsive to treatment to reach the premaintenance evaluation. These factors obviously limit the generalizability of our results and make it impossible to address certain questions even in our own sample (e.g., the influence of personality features on attrition during acute treatment). At the same time, the current approach allows us to place more confidence in the personality assessments that were available; in the future, we will also be able to examine prospectively the relationship between personality and recurrence during maintenance therapy. In addition, given that our measures of personality have some validity, we are encouraged to extend their use to other prospective questions (e.g., attrition and failure to respond during acute treatment, rapid relapse after initial response) and to other samples. To attenuate the impact of acute depressive symptoms on personality ratings, the Personality Assessment Form can be used in conjunction with the structured interviews (27, 28) currently available for personality diagnosis. These interviews include versions for both patients and their significant others. The use of an informant (29) is an additional strategy that may make it possible to collect personality data which are more clearly reflective of trait characteristics of the patient as opposed to features of the depressive state.

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APPENDIX 1. Inventory and Scale Components of the Hirschfeld-Klerman Personality Battery

I. Guilford-Zimmerman Temperament Survey: General Activity, Restraint, Ascendance, Sociability, Emotional Stability, Objectivity, and Thoughtfulness

II. Interpersonal Dependency Inventory: Emotional Reliance on Another Person, Lack of Social Self-Confidence, and Assertion of Autonomy

III. Lazare-Klerman-Armor Personality: Obsessionality, Hysterical Pattern, and Orality

IV. Maudsley Personality Inventory: Neuroticism and Extraversion

V. Minnesota Multiphasic Personality Inventory: Ego Control and Ego Resilience

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The office of the *American Journal of Psychiatry* and *Psychiatric News* will be in room 318 of the Montreal Convention Center. The office will be open Sunday, May 8, 10:00 a.m.–5:00 p.m., and Monday–Thursday, May 9–12, 8:00 a.m.–5:00 p.m.

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Cerebral Blood Flow Changes During Sodium-Lactate-Induced Panic Attacks

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Lynda Lane, M.S., R.N., and Frederick J. Bonte, M.D.

Dynamic single-photon emission computed axial tomography (CAT) with inhaled xenon-133 was used to measure regional cerebral blood flow in 10 drug-free patients with DSM-III-*diagnosed panic disorder and in five normal control subjects. All subjects underwent regional cerebral blood flow studies while at rest or during normal saline infusion and during sodium lactate infusion. Six of the 10 patients and none of the control subjects experienced lactate-induced panic attacks. Lactate infusion markedly raised hemispheric blood flow levels in both control subjects and patients who did not panic. Patients who did panic experienced either a minimal increase or a decrease in hemispheric blood flow.*

(Am J Psychiatry 1988; 145:442–449)

High-resolution brain imaging techniques suitable for study of metabolic changes in emotional disorders have been developed in this decade (1–3). The distinct quality of the symptoms of panic attacks and the well-defined episodes of such attacks especially lend themselves to study by brain imaging. Redmond (4) hypothesized that the symptoms of anxiety result from the activation of the locus ceruleus in the pons. The locus ceruleus contains primarily noradrenergic neurons that send afferent projections to the hippocampus, hypothalamus, limbic area, and ultimately the cerebral cortex (5, 6). Halgren et al. (7) induced emotional and vegetative symptoms of panic disorder by stimulation of the amygdala and hippocampal gyrus. Electric stimulation of the right temporal lobe has also been associated with altered feeling states, anxiety, and depression (8). More recently, using positron emission tomography (PET), Reiman et al. (9) demonstrated abnormally low ratios of left-to-right parahippocampal blood flow in patients who were vulnerable to lactate-induced panic attacks.

The purpose of the present study was to determine if any localized neuronal activation occurs in the cerebral cortex during panic attacks. Changes in regional cerebral blood flow closely parallel neuronal metabolism and can therefore be used to determine regional neuronal excitation (10–12). In this study we determined changes in regional cerebral blood flow during lactate-induced panic attacks in several predetermined cortical regions of the brain by using dynamic single-photon emission computerized axial tomography (CAT).

METHOD

Subjects

Ten patients with *DSM-III* diagnoses of panic disorder with or without agoraphobia were studied. Individuals who met criteria for concurrent major depression or who had a recent history of substance abuse were excluded from the study. All subjects had normal results for CBCs and differential counts, SMA-20s, thyroid function tests, and EKGs. Patients were recruited either through advertisement or from the psychiatric emergency room. The five control subjects were volunteers from the university staff. All subjects signed informed consent forms according to the guidelines of the Institutional Review Board of the University of Texas Health Science Center at Dallas.

Only patients who had never been treated with tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), or alprazolam were accepted for the study. Seven patients had been totally drug free for more than a month before the start of the investigation. Two patients had been receiving oxazepam up to 48 hours and one patient had been receiving clorazepate up to 24 hours before the baseline study. All patients and control subjects were in good health, and

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all (except for one female control subject) were right-handed.

Subjects were diagnosed by using the Structured Clinical Interview for *DSM-III*, Upjohn Version (13), a modified version of the Structured Clinical Interview for *DSM-III* developed by Spitzer and Williams specifically for the accurate diagnosis of panic disorder.

At initial evaluation, subjects were assessed by using the Hamilton Rating Scale for Anxiety, the 17-item Hamilton Rating Scale for Depression, the Sheehan Patient-Rated Anxiety Scale (14), the Phobia Scale (14), and a panic symptom checklist. Their current and past medical and psychiatric histories were also obtained and laboratory and EKG studies were carried out.

Dynamic Single-Photon Emission CAT

Regional cerebral blood flow was determined by dynamically monitoring the cerebral transit of xenon-133 with the Tomomatic-64 dynamic single-photon emission CAT (Medimatic A/S, Copenhagen, Denmark) designed by Stokely et al. (15). This tomograph consists of four detector arrays, each containing 16 NaCl (T_1) scintillation crystals. The arrays are mounted in a hollow-square configuration that rotates around the subject's head at 6 rpm. Special focused collimators define three transverse tomographic cross-sections with centers 4 cm apart. Xenon-133 is administered in an air-oxygen mixture (10 mCi/liter) during the first minute of a 4-minute washin/washout procedure. The patient breathes room air during the remaining 3 minutes of the study, exhaling the mixture into a charcoal trap. During the 4-minute measurement period, activity in the lung is monitored by a scintillation probe placed on the patient's chest, and this activity is assumed to correspond to the arterial blood concentration of xenon-133 in the brain. Detected radiation data are transmitted through an optical link to a Univac V77 computer, which generates the three tomographic cross-sections by filtered back projection with attenuation correction according to the method of Kay and Keyes (16). Regional cerebral brain flow is calculated in milliliters per minute per 100 g according to the double-integral method described by Kanno and Lassen (17), Celsis et al. (18), and Smith et al. (19). The reproducibility and reliability of this method have been evaluated in normal subjects by Devous et al. (20).

Voxel flow values are displayed in a 64-by-64 matrix using a 16-shade scale that can be normalized to the highest flow value. System resolution (full width at half maximum) measured with a xenon-133 line source in water varies from 1.7 cm at the center of each slice to 1.0 cm at the edge transversely. The focusing collimator design keeps axial resolution almost constant at 1.9 cm. System sensitivity measured for xenon-133 in water in a 17-cm-diameter cylindrical phantom is 19,700 counts/mCi per ml per slice. The scatter fraction is 30%–40% for xenon-133.

Subjects are studied with their eyes open and their ears unplugged. The room is dimly lit and background noise originates primarily from instrument cooling fans. Subjects breathe through a fitted mouthpiece; their nostrils are occluded by a spring clamp. Approximately 2 minutes of adaptation time is allowed before initiating the study. Each subject is asked to take a deep breath at the beginning of the study, after which no further communication occurs. Subjects are positioned in the tomograph so that the three transverse cross-sections are located at 2, 6, and 10 cm above and parallel to the canthomeatal line. Positioning for the study is accomplished by marking a reference line on the subject's face that is aligned with the tomograph frame.

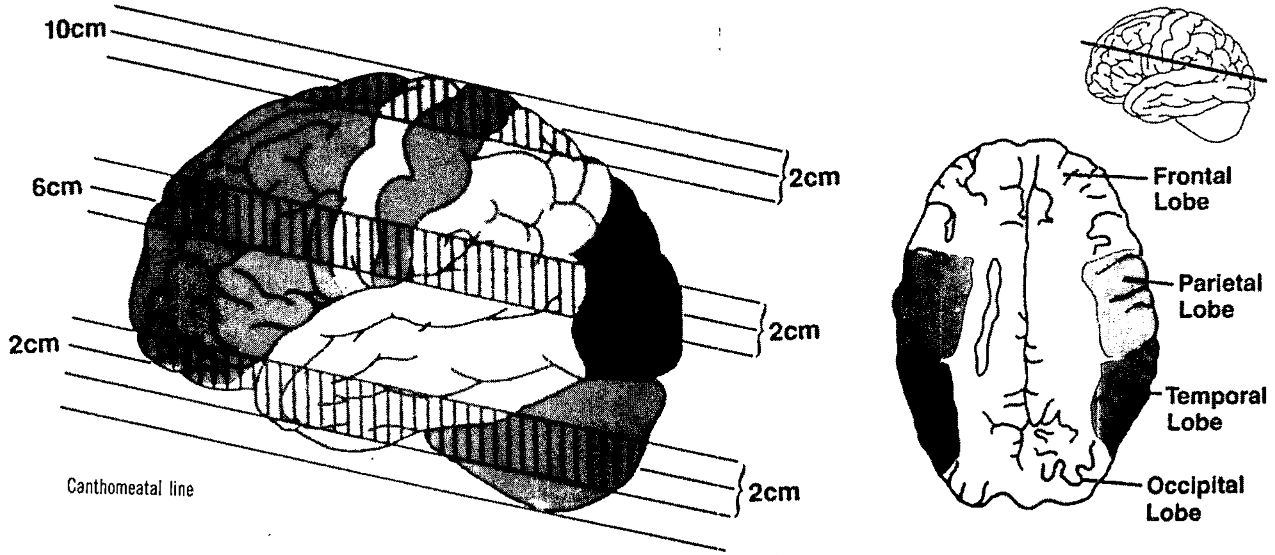
Regional cerebral blood flow images are transferred from the V77 computer to a Perkin-Elmer 3241 computer employing a Genisco 512-by-512-by-8-bit GCT-3000 frame buffer, a Talos Cybergraph graphics tablet, and a Textronix 670-A-1 color monitor used with interactive graphic software to obtain digital regional cerebral blood flow values from images as described in detail by Stokely et al. (21). Briefly, regional cerebral blood flow images are scaled, rotated, and translated to match a predefined standard brain outline that includes a graphic overlay of regions of interest defined from a CAT cross-sectional brain atlas taken at the same level as the regional cerebral blood flow images. Regional flows and their standard deviations are obtained from frontal, parietal, superior temporal, occipital, and central gray matter as well as from white matter and from both hemispheres by using the slice 6 cm above the canthomeatal line. The automatic fitting routine produces standard scaling and reproducible regions of interest so that operator intervention has a minimal effect on results. Figure 1 shows the areas of interest and the three transverse cross-sections.

Regional cerebral blood flow was measured in a randomized sequential design so that each subject served as his or her own control. Observed changes in regional cerebral blood flow between study conditions thus depend only on subject physiology, minimizing the limitations of this technique. Devous et al. (20) demonstrated that this method is reproducible and reliable for sequential measurement studies in normal volunteers when sequential measurements are made hours to weeks apart.

Study Design

The first three patients underwent three scannings each: during the resting state, after saline infusion with 10 ml of normal saline per kilogram of body weight, and after sodium lactate infusion with 10 ml of 0.5 M sodium lactate per kilogram of body weight. Since data from these three patients revealed no difference in regional cerebral blood flow during the resting state and during saline infusion, the remaining seven patients and the five control subjects were randomly

FIGURE 1. Transverse Cross-Sections and Cerebral Areas Studied in 10 Patients With Panic Disorder and Five Normal Control Subjects



assigned to either a resting state or saline infusion for baseline study to minimize radiation exposure for each subject. The remaining patients and the control subjects thus underwent two scannings each rather than three.

Sodium lactate infusions were given as fast as possible and were completed within 20–30 minutes. When a patient experienced a panic attack the sodium lactate infusion was lowered to 2–3 drops/minute. The xenon scan was performed after the lactate infusion was completed or after the patient experienced a panic attack, whichever came first.

During the procedure subjects were reclining in a supine position in a quiet, dimly lit room; each had an intravenous line in the left arm. They were instructed to keep their eyes open. The maximum amount of fluid infused was 1000 cc per session. The scans were performed on separate days. Pulse rate was monitored during each scan. Immediately after the scan, each patient was evaluated with the Hamilton anxiety scale and the Sheehan Patient-Rated Anxiety Scale, and a panic symptom checklist was completed by an experienced psychiatrist (R.S.S.).

The Sheehan Patient-Rated Anxiety Scale rates 12 items on a 5-point scale on which 0=symptoms not present and 4=very severe symptoms; total scores on the scale range from 0 to 48. The Phobia Scale allows patients to identify four specific phobias in addition to the fear of leaving home. Fear is rated on a 10-point scale on which 1–3=mild, 4–6=moderate, 7–9=marked, and 10=extremely severe symptoms. Avoidance is rated on a 5-point scale on which 0=never and 4=always. Total scores on the Phobia Scale range from 0 to 70. The panic symptom checklist identifies the presence or absence of the 12 symptoms of a panic attack as they are listed in *DSM-III*.

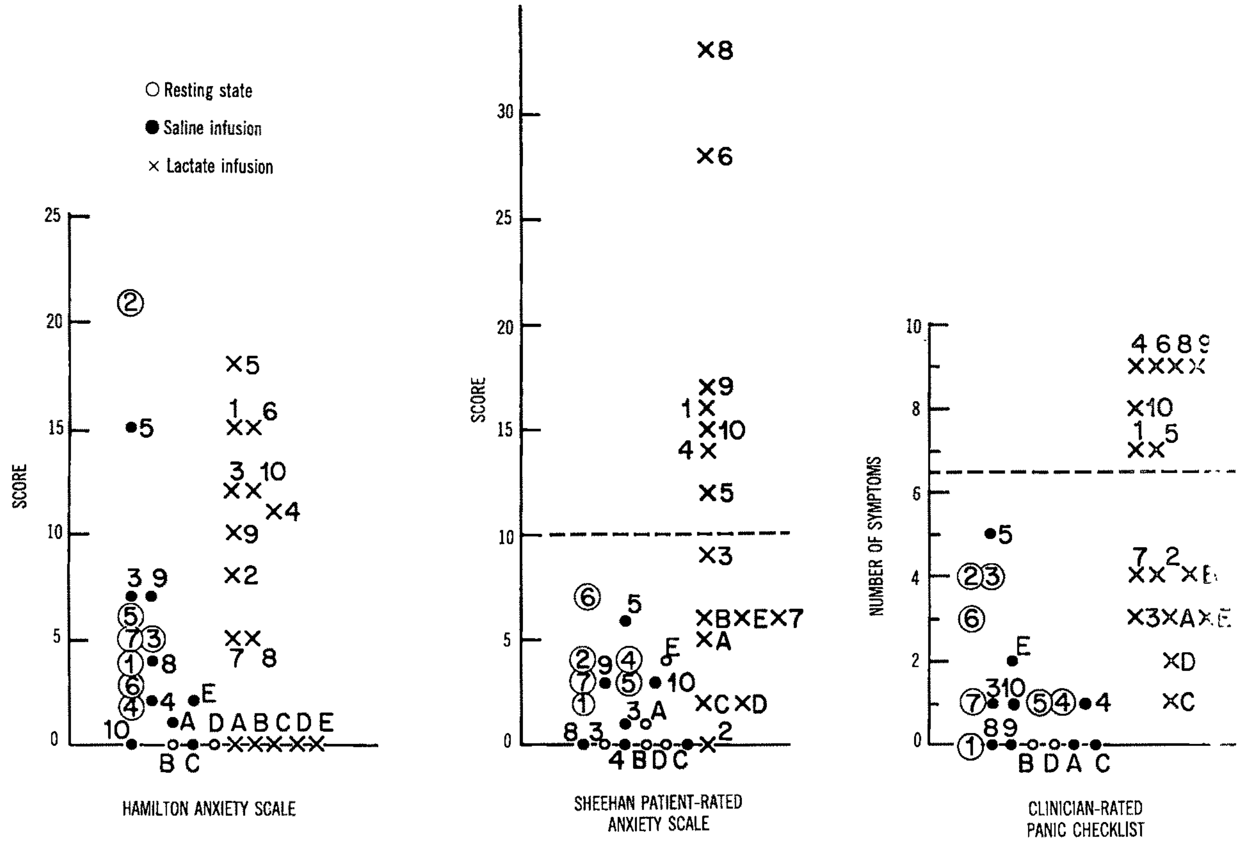
RESULTS

Six of the 10 patients (one man and five women) panicked during sodium lactate infusion; their mean±SD age was 34.3±11.3 years. Four patients (two men and two women) did not panic during sodium lactate infusion; their mean±SD age was 34.2±7.4 years. None of the control subjects (one man and four women) panicked; their mean±SD age was 31.6±4.8 years. Analysis of variance (ANOVA) between the patients who panicked, the patients who did not panic, and the control subjects did not indicate any significant group differences in age (F=0.18, df=2, 12, p=.838).

The Sheehan Patient-Rated Anxiety Scale and the clinician-rated panic symptom checklist were used to define the presence of a panic attack during infusion. The change in number of symptoms from baseline (during the resting state and/or during saline infusion) to lactate infusion rather than raw scores was used to define panic (figures 2–4). To ensure that a panic attack had occurred we used an increase of at least four symptoms and an increase of greater than 6 points in the Sheehan Patient-Rated Anxiety Scale. The raw scores were not used because individuals with high anticipatory anxiety not related to a panic attack may report higher scores on the Sheehan Patient-Rated Anxiety Scale. Use of the change in scores rather than the use of raw scores allowed us to control for subjects' variable experiences of anticipatory anxiety. Using these criteria, we designated two patients who reported "near panic" and "mild panic" as not having a panic attack.

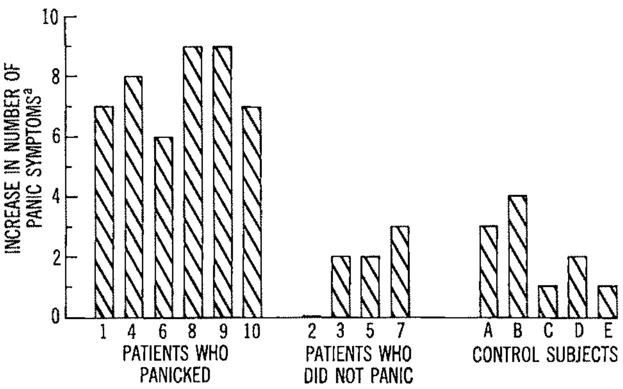
The patients' scores on the Hamilton anxiety scale appeared to reflect their level of anticipatory anxiety rather than their level of panic and therefore was not

FIGURE 2. Raw Scores of 10 Patients With Panic Disorder and Five Normal Control Subjects on Three Measures of Anxiety or Panic Symptoms at Baseline (Resting State and/or Saline Infusion) and During Sodium Lactate Infusion[a]



[a]Individual patients are indicated by numbers 1–10; individual control subjects are indicated by letters A–E.

FIGURE 3. Increase in Number of Panic Symptoms From Baseline (Resting State and/or Saline Infusion) to Sodium Lactate Infusion in 10 Patients With Panic Disorder and Five Normal Control Subjects



[a]Rated with the clinician-rated panic checklist.

an appropriate instrument to define a panic attack (figure 2).

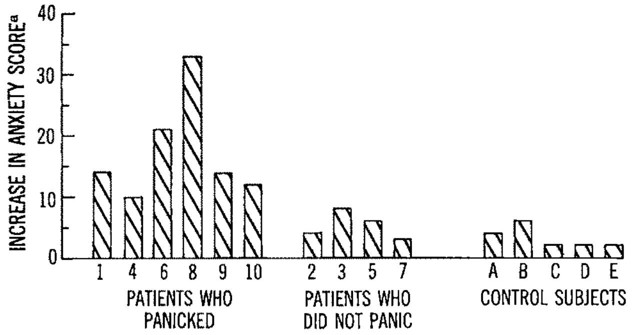
No control subjects met criteria for panic on the Sheehan Patient-Rated Anxiety Scale and the panic checklist, and none reported the subjective experience of panic. Several control subjects experienced shivering, cold chills, and mild perioral numbness during the sodium lactate infusion. None reported dizziness, shortness of breath, or palpitations in spite of the fact that the pulse meter recorded substantial increases in heart rate.

Regional cerebral blood flow was determined by an analysis scheme developed by Stokely et al. (21). Regional cerebral blood flow was standardized by dividing the regional flow values by the hemispheric cerebral blood flow. Change in blood flow was determined for frontal, temporal, parietal, occipital, and superior temporal areas bilaterally between baseline (resting state and/or saline infusion) and sodium lactate infusion.

A one-way ANOVA followed by the Student-Newman-Keuls multiple comparison procedure was used to compare blood flows for the patients who panicked, the patients who did not panic, and the control subjects for each region separately. An overall 0.05 significance level was accepted as significant for the Student-Newman-Keuls comparisons. In the left hemisphere, results of the ANOVA for percent change in total cerebral blood flow were more significant than in the right hemisphere (left: F=5.98, df=2, 12, p=0.016; right: F=4.73, df=2, 12, p=0.031).

In the left hemisphere the change in total hemi-

FIGURE 4. Increase in Anxiety Scores From Baseline (Resting State and/or Saline Infusion) to Sodium Lactate Infusion in 10 Patients With Panic Disorder and Five Normal Control Subjects



[a] Score on the Sheehan Patient-Rated Anxiety Scale.

TABLE 1. Percent Change in Hemispheric Cerebral Blood Flow in 10 Patients With Panic Disorder and Five Normal Control Patients From Baseline (Resting State and/or Saline Infusion) to Sodium Lactate Infusion

	Change in Cerebral Blood Flow (%)	
Subjects	Left Hemisphere	Right Hemisphere
Patients who panicked (N=6)	+2.9[a]	+1.5[b]
Patient 1	+9.5	+7.6
Patient 4	+5.0	+1.1
Patient 6	+17.1	+12.0
Patient 8	+1.0	0.0
Patient 9	−6.2	+4.1
Patient 10	−9.2	−15.6
Patients who did not panic (N=4)	+24.8	+21.8
Patient 2	+25.0	+22.4
Patient 3	+20.5	+20.2
Patient 5	+19.1	+16.7
Patient 7	+34.8	+27.9
Control subjects (N=5)	+20.4	+19.7
Subject A	0.0	−2.4
Subject B	+22.9	+18.7
Subject C	+28.6	+32.9
Subject D	+14.2	+9.7
Subject E	+36.5	+39.7

[a] Significantly greater than the changes in the other two groups ($p<0.05$, Student-Newman-Keuls procedure).

[b] Difference from changes in the other two groups approached significance ($0.05>p<0.10$, Student-Newman-Keuls procedure).

spheric blood flow was significantly greater in the five control subjects and the four patients who did not panic than in the six patients who experienced panic attacks (table 1). For the right hemisphere the change in total hemispheric blood flow was greater in patients who did not panic and control subjects than in patients who experienced sodium-lactate-induced panic attacks, but the difference was of borderline significance (table 1).

In addition, one-way ANOVA demonstrated a significantly greater increase in regional cerebral blood flow in the right occipital region (F=7.25, df=2, 12, p=0.009) and the left occipital region (F=3.73, df=2, 12, p=0.055) in patients who panicked than in patients who did not panic and control subjects (table 2).

A trend for decreased left frontal blood flow during panic was noted but did not reach statistical significance (F=2.02, df=2, 12, p=.175). No statistically significant changes were noted in any other region of interest (table 2).

One-way analyses of covariance were performed for the left and right occipital regions and for each hemisphere with baseline (resting state and/or saline infusion) blood flow as the covariate and blood flow during sodium lactate infusion as the dependent variable. The increase in left hemispheric blood flow in control subjects and patients who did not panic was almost statistically significantly greater than that of patients who panicked (F=3.84, df=2, 1, p=0.054).

Pearson's correlation coefficients were computed for the change in panic scores and the change in blood flow for left and right hemispheres and occipital lobes in each group. This analysis did not reveal any correlation between severity of panic attack and increase in cerebral blood flow.

DISCUSSION

The search for anatomical correlates of panic attacks depends on accurate definition and replication of "spontaneous" panic attacks and the accurate visualization of brain regions suspected of mediating anxiety—the limbic area with its frontal projections.

Margraf et al. (22) highlighted the difficulty in determining when a patient panics and criticized the subjective and poorly defined criteria used by investigators. They contended that laboratory-induced panic attacks are generally of moderate intensity compared with naturally occurring ones and may not be the same phenomena (22). Only carefully designed patient and clinician rating scales can document that naturally occurring panic attacks result in the identical subjective and symptomatic changes as those induced by sodium lactate.

Fortuitously, one of our patients (patient 1) had a spontaneous "natural" panic attack in the laboratory. He had seven documentable symptoms of panic, compared with nine symptoms in four patients with lactate-induced attacks and eight symptoms in one patient with lactate-induced attacks. Similarly, on the subjective Sheehan Patient-Rated Anxiety Scale, patient 1 reported a score of 16, compared with scores of 14, 28, 33, 17, and 15 reported by the patients with lactate-induced panic attacks. Thus, our findings suggest that the severity of the lactate-induced panic was at least as intense as the naturally occurring ones if not more so.

Devous et al. (20) demonstrated that regional cerebral blood flow is higher in women than in men at all ages and that with aging there is a slight decline in regional cerebral blood flow for both sexes in all

TABLE 2. Regional Cerebral Blood Flow in 10 Patients With Panic Disorder and Five Normal Control Subjects at Baseline (Resting State and/or Saline Infusion) and During Sodium Lactate Infusion

	Cerebral Blood Flow (ml/100 g of tissue per minute)											
	Left Hemisphere		Right Hemisphere		Left Frontal		Right Frontal		Left Occipital		Right Occipital	
Subjects	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients who panicked (N=6)												
Resting state or saline infusion	84	14	88	13	86	16	87	13	84	17	91	20
Panic or lactate infusion	86	9	89	10	82	8	83	8	85	12	93	16
Patient 1												
Resting state	63	15	66	12	65	10	68	8	56	10	60	8
Spontaneous panic attack	69	13	71	12	67	10	69	10	65	11	65	10
Patient 4												
Saline infusion	80	16	85	15	79	11	82	10	87	22	88	13
Lactate infusion	84	16	86	14	82	10	81	12	80	26	94	21
Patient 6												
Resting state	76	18	83	15	79	16	83	13	71	19	79	15
Lactate infusion	89	20	93	17	89	21	93	13	89	28	96	21
Patient 8												
Saline infusion	92	20	97	18	88	17	89	17	98	25	105	20
Lactate infusion	93	24	97	19	81	20	85	14	99	25	108	22
Patient 9												
Saline infusion	96	20	96	21	98	21	93	22	94	23	105	27
Lactate infusion	90	19	100	21	84	13	87	19	90	27	108	29
Patient 10												
Saline infusion	98	19	103	19	109	16	108	17	96	17	113	20
Lactate infusion	89	18	87	19	89	19	83	13	88	18	88	21
Patients who did not panic (N=4)												
Resting state or saline infusion	70	3	74	5	66	4	68	6	71	6	80	4
Lactate infusion	87	4	90	5	82	4	79	6	90	5	93	7
Patient 2												
Resting state	72	17	76	14	65	18	66	14	72	17	81	12
Lactate infusion	90	14	93	14	85	11	85	7	92	20	95	15
Patient 3												
Saline infusion	73	14	79	15	69	11	74	12	80	18	87	16
Lactate infusion	88	22	95	23	86	11	83	11	96	28	102	29
Patient 5												
Saline infusion	68	15	72	16	68	13	70	17	68	16	78	18
Lactate infusion	81	18	84	17	79	13	78	13	88	27	88	24
Patient 7												
Resting state	66	15	68	14	61	13	61	11	66	17	77	18
Lactate infusion	89	25	87	21	77	14	72	16	84	29	86	24
Control subjects (N=5)												
Resting state or saline infusion	76	11	78	11	76	15	75	16	80	11	86	11
Lactate infusion	93	8	92	8	91	7	86	8	87	13	92	8
Subject A												
Saline infusion	85	18	85	20	86	11	82	9	85	25	98	23
Lactate infusion	85	14	83	16	89	13	83	15	72	15	84	13
Subject B												
Resting state	74	12	75	14	73	11	75	11	81	13	84	12
Lactate infusion	91	17	89	19	86	10	81	16	83	15	87	14
Subject C												
Saline infusion	70	13	73	15	64	10	61	11	74	8	82	9
Lactate infusion	99	18	97	19	98	17	95	16	107	24	104	22
Subject D												
Resting state	91	17	93	19	97	17	99	21	95	15	97	20
Lactate infusion	104	20	102	18	99	16	95	13	94	20	98	13
Subject E												
Saline infusion	63	16	63	14	60	18	59	16	66	16	71	13
Lactate infusion	86	17	88	17	83	12	80	13	81	19	88	16

regions of the brain. Therefore, we carefully controlled for the age and sex distribution of each of our study groups.

In our study cerebral blood flow was standardized to whole hemispheric blood flow. Using this method we found a statistically significantly greater increase in regional cerebral blood flow in the right occipital area of patients who panicked than in that of patients who did not panic and that of normal control subjects. The regional cerebral blood flow increase found in the left occipital region of the patients who panicked did not reach statistical significance. It is unlikely that these changes are a consequence of head movement or other artifacts because no statistically significant changes were observed in control subjects and this method has been validated to be reproducible for repeat measurements separated by hours to weeks (20).

Using PET, Buchsbaum et al. (23) demonstrated a significant decrease in glucose metabolism in the occipital lobe of patients with generalized anxiety disorder after 21 days of treatment with clorazepate. They controlled for hypervigilant attention in patients by requiring them to perform a visual vigilance task during the uptake of the radioactive deoxyglucose. Their findings were similar to ours in that there was a greater change in the right occipital rather than in the left occipital region. Buchsbaum et al. attributed the increased metabolic activity of the right occipital lobe during anxiety to the high-density benzodiazepine receptors in this region. The greater right than left metabolic activity is similar to the asymmetry observed in cerebral blood flow by Mathew et al. (24) after diazepam administration.

Activation of the occipital cortex could be also attributed to spacious visual scanning during panic attacks. This is not likely because visual stimulation is accompanied by increased regional cerebral blood flow in the frontal eye fields and the supplementary motor area of the frontal cortex (25), a phenomenon not observed in our patients.

Curtis et al. (unpublished 1986 paper) reported a small area of increased blood flow in the anterior inferior medial portion of the temporal lobe during panic attacks induced by the presentation of phobic stimulus. We did not observe such changes in our patients. However, one should note that Curtis et al. studied phobic patients rather than patients with panic disorder.

The rest of the regions of interest studied did not show any regional blood flow changes with the exception of the frontal area, where there was a tendency for decreased regional blood flow that was greater on the left than on the right. Using PET, Reiman et al. (9) reported abnormally low ratios of left-to-right parahippocampal blood flow during the resting state in patients susceptible to lactate-induced panic attacks. We were not able to replicate the findings of Reiman et al. because the parahippocampal area was not visualized in our study.

Our finding of a significant increase in hemispheric blood flow during sodium lactate infusion in control subjects and in patients who did not experience lactate-induced panic is similar to the finding of increases in metabolism reported by Reiman and Raichle in nonpanicking patients and control subjects studied with PET (personal communication). Increased blood flow may be secondary to a sodium-lactate-induced increase in serum bicarbonate, increased plasma volume, or, to a lesser extent, resultant hemodilution.

Schieve and Wilson (26) demonstrated that an isotonic infusion of 1.2% sodium bicarbonate will result in a 30% increase in cerebral blood flow but that an equal volume of isotonic normal saline will not affect cerebral blood flow. Our findings are similar to theirs in that we found a 20%–23% increase in cerebral blood flow with sodium lactate and none with an equal amount of normal saline. During sodium lactate infusion there is a significant increase in serum bicarbonate level as a result of oxidative conversion of lactate to bicarbonate (27). Bicarbonate dissociation into CO_2 results in elevated cerebral CO_2 levels, decreased cerebral vascular resistance, and increased cerebral blood flow. Hypertonic saline (2% NaCl) infusion results in some increase in cerebral blood flow, but it is less marked than that of bicarbonate (26). One would expect some increase in cerebral blood flow from the hypertonicity of sodium lactate alone and, possibly, to a lesser extent from the resultant hemodilution. Gaffney et al. (28) documented marked increase in heart rate, stroke volume, and cardiac output in normal subjects following 0.5 M sodium lactate infusion.

Patients experiencing lactate-induced panic showed a minimal increase or an actual decrease in total cerebral blood flow. Two mechanisms might account for this finding: 1) higher baseline cerebral blood flow at rest in patients prone to lactate-induced panic and 2) cerebral vasoconstriction of such magnitude as to overcome lactate-induced increase in blood flow.

Reiman et al. (9) reported a trend toward increased whole brain blood flow and elevated whole brain oxygen metabolism in patients at rest who are susceptible to lactate-induced panic. Our data confirm their finding of a tendency for increased whole brain blood flow at baseline in patients vulnerable to lactate-induced panic. Nevertheless, the increased baseline whole brain blood flow in our study was minimal and therefore does not appear to account for the minimal increase or the apparent decrease in whole brain blood flow during panic attack.

There was either a minimal increase or an actual decrease in whole brain blood flow during panic attacks. Panic attacks are usually accompanied by hyperventilation, which leads to a decrease in P_{CO_2} and results in acute respiratory alkalosis (29–31). Changes in P_{CO_2} affect cerebral blood flow more than any other factor (32, 33). Although pH changes have minimal effect on cerebral blood flow, there is a significant linear relationship between cerebral blood flow and P_{CO_2} (34, 35). The responsiveness of cerebral blood flow to acute changes in P_{CO_2} is related to cerebral vascular resistance: the lower the P_{CO_2} the more vasoconstriction will occur (36, 37). Using a bidirectional, pulsed ultrasound Doppler blood velocity meter, Hauge et al. (38) calculated that during hyperventilation in humans the percent blood flow decrease to the brain was 3.92%/mm Hg. The greatest drop in cerebral blood flow occurred during the first 3 minutes of hyperventilation (38). Gorman et al. (27) demonstrated that lactate infusion alone lowered P_{CO_2} values, but the greatest drop occurred in patients who panicked. Thus, the decrease in whole brain blood flow in patients who panicked could be attributed to a large extent to lower P_{CO_2} secondary to hyperventilation.

CONCLUSIONS

Since we did not monitor arterial P_{CO_2} changes during our study we cannot state conclusively whether hypocapnia alone explained the decrease in whole brain blood flow during panic attacks.

Sodium-lactate-induced panic attacks can be well defined by using appropriate rating scales, and they can be of the same intensity as spontaneous or "naturally" occurring panic attacks.

Panic attacks appear to be accompanied by a significant increase in regional cerebral blood flow in the right occipital region.

Sodium lactate produced a 20%–23% increase in whole brain blood flow in normal control subjects and in patients with panic disorder who did not panic but led to only a 2.2% increase in whole brain blood flow in patients with panic disorder who panicked with lactate infusion.

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Court-Mandated Community Outpatient Treatment for Persons Found Not Guilty by Reason of Insanity: A Five-Year Follow-Up

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The authors conducted a 5-year follow-up study of 79 persons found not guilty by reason of insanity who were referred to and accepted for court-mandated community outpatient treatment. This was a severely mentally ill and violent group with extensive experience in both the criminal justice and mental health systems. This program was not without risks despite a readiness to revoke the patients' conditional release status when indicated; during the 5-year follow-up period, 25 (32%) were rearrested (18 [72%] for crimes of violence), 37 (47%) were hospitalized, and 38 (48%) had their conditional releases revoked. The authors believe that members of this population need social controls and long-term treatment when they are in the community.

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What should happen to mentally ill persons who commit serious criminal acts? Hospitalization provides a temporary solution, but how can we meet the needs of these persons after their discharge into the community and still protect society? This study explores the outcomes for persons found not guilty by reason of insanity who were consecutively referred to and accepted for court-mandated community outpatient treatment provided under California's Conditional Release Program for the Judicially Committed. All of the subjects were studied for a period of 5 years after referral to court-mandated community outpatient treatment. What was the outcome for these persons in terms of rearrests, hospitalizations, and revocations of their provisional releases from hospitals for mandatory outpatient treatment?

Oregon, Illinois, and Maryland have community treatment programs specifically designed for the person found not guilty of a crime by reason of insanity. The program in Oregon has a number of innovative aspects and has also been well described (1, 2). Rogers and Bloom (1) reported the Oregon system as preserving "the medical, moral, and legal values of the insanity defense, while simultaneously honoring the growing contemporary consensus that security measures should be substantially improved for insanity acquittees." Oregon has established a Psychiatric Security Review Board whose primary goal, as directed by statute, is the protection of society. Thus, prompt revocation of a patient's release into the community when indicated is emphasized. Moreover, the Psychiatric Security Review Board has jurisdiction over the patient for a period as long as the term of the maximum sentence he or she would have served if found guilty. The Oregon system, in addition to emphasizing security measures, stresses continuing treatment of released patients as well as the use of supportive services.

The results of Oregon's program have been systematically studied (2). In the first 3 years of the Psychiatric Security Review Board's operation, 165 persons were conditionally released into community programs. Of these, 10% were charged with new crimes (4% felonies and 6% misdemeanors) and 40% had their conditional releases revoked, primarily as a result of deterioration of their mental health status. At the end of the first 5 years of the Psychiatric Security Review Board's operation, 295 persons had been conditionally released at least once. This represented 47% of those under Psychiatric Security Review Board jurisdiction. Of these, 6% were charged with new felonies and 7% with new misdemeanors. According to Rogers et al. (1, 2), the Psychiatric Security Review Board system in Oregon has not only provided uniform, predictable, and effective community treatment and support programs for chronically mentally ill and dangerous offenders but has also provided the community with adequate security from mentally ill offenders. By facilitating conditional release, this system has also helped to ease hospital overcrowding.

Cavanaugh and Wasyliw (3) studied 44 persons who had been found not guilty by reason of insanity in Illinois. The majority had committed murder or attempted to murder a family member or someone else known to them. All 44 subjects had been discharged from inpatient settings, were in court-mandated out-

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patient treatment, and were assessed for 19 months. Seventy-nine percent were considered to have major mental disorders. During the 19-month study period, there was no recidivism for crimes against persons; the rate of rehospitalization was approximately 25% per year.

In Maryland, persons found not guilty by reason of insanity for felonies are given a 5-year conditional release at the time of their hospital discharge (4). Spodak et al. (5) studied 91 such subjects who had been in the community for at least 5 years. Sixty had been in the community 5–10 years since their hospital discharge and 31 for 10–15 years. Reliable data were available for 86 of the 91 subjects. Of these, 48 (56%) had been *rearrested* for new crimes. Four of those rearrested were found not guilty by reason of insanity again. Of the remaining 82 subjects, 26 (32%) were *convicted* of new crimes. Most of the subsequent charges were less serious than the charges of which they had originally been found not guilty by reason of insanity. For the group as a whole, there was also a reduction in arrest rates, which were two and a half times less frequent after their conditional releases than they had been before. According to Spodak et al. (5), their study demonstrated that Maryland's policy of at least 5 years' supervised follow-up and possible extension of conditional release for "cause" is appropriate.

In reviewing the literature on the insanity defense and the present state of this defense throughout the United States, Weiner (6) made the following recommendations as "model legislation": that jurisdiction over persons found not guilty by reason of insanity remain in the criminal court rather than in the civil court, that the likelihood of dangerousness in the near future not be a requirement for such jurisdiction (as it is in civil courts), that there be provision for supervised outpatient care, and that outpatient mental health facilities be able to treat with broad discretion.

In 1975, statutes were enacted in California that provided funding for 18 state-wide community (county) outpatient treatment programs for judicially committed patients. These programs were referred to as the Conditional Release Program for the Judicially Committed (7). One of the patient groups served by the Conditional Release Program is persons found not guilty by reason of insanity.

If a defendant in California is found not guilty by reason of insanity, he or she is acquitted of the criminal charge. However, unless it appears to the court that this person has recovered his or her sanity fully (i.e., has improved to such an extent that the person is no longer a danger to the health and safety of others and self), he or she will be transferred to the jurisdiction of the mental health system. The maximum term of commitment of a person found not guilty by reason of insanity is determinate: it is as long as the maximum term of imprisonment for the offense if the person had been found guilty. In most cases, defendants who have been found not guilty by reason of insanity suffer from serious psychiatric disorders and have committed felonies. Consequently, these people are almost always placed in secure psychiatric facilities, such as forensic state hospitals, after their acquittal by reason of insanity.

These patients may be released from the hospital if 1) they prove to the court that their sanity has been restored, 2) their term of commitment has expired, or 3) they are transferred to continued treatment and supervision in the Conditional Release Program for the Judicially Committed. A patient's maximum term of commitment can also be extended indefinitely for 1- or 2-year intervals if the patient was committed for a felony and if he or she represents a substantial danger of physical harm to others because of mental illness. Such extensions are often very difficult to obtain, especially if there have been repeated extensions.

Because of the nature of the treatment and supervision provided by the Conditional Release Program, both the forensic hospital treatment staff and the courts seem inclined to place patients in court-mandated community outpatient treatment programs rather than simply keeping them in the hospital until their term of commitment has expired or their sanity has been restored and then having to release them unconditionally. Patients who decompensate, refuse to cooperate with their treatment plan, or become dangerous to others may have their outpatient status revoked and be returned to the forensic hospital to continue serving their term of commitment.

METHOD

The study population consisted of all persons from Los Angeles County who from July 1, 1979, to December 31, 1980, had been found not guilty by reason of insanity and who, for the first time, had been referred to and then accepted for court-mandated community outpatient treatment. This period was selected for two reasons: 1) the court-mandated community outpatient treatment program had started in 1975 and was well established by July 1979 and 2) it allowed for a 5-year follow-up period from the point of referral to the end point of the study, December 31, 1985.

During the period from July 1, 1979, to December 31, 1980, 101 persons found not guilty by reason of insanity were referred for the first time to court-mandated community outpatient treatment; 9 of these persons were not accepted into the court-mandated community outpatient treatment program. Eighty-two persons were referred and accepted during this period. Two of those who entered court-mandated community outpatient treatment died of natural causes and one committed suicide while they were in such treatment. The 5-year follow-up group thus numbered 79.

Extensive records of all persons referred to and accepted for court-mandated community outpatient treatment are maintained by the Conditional Release Program of the Los Angeles County Department of Mental Health. Treatment in the particular program we studied is characterized by a reality-based approach and a focus on the problems of everyday living. The principles of case management, an emphasis on structure and supervision, extensive use of neuroleptic medications, and close involvement with the criminal justice system are incorporated into the treatment.

Records available for this study included police and arrest reports, psychiatric reports prepared for determinations of not guilty by reason of insanity, and hospital summaries that usually included the patient's past psychiatric history and criminal record, information about the offense of which the patient was found not guilty, the patient's behavior and progress in the hospital, and the patient's psychiatric diagnosis. Evaluation for suitability for court-mandated community outpatient treatment conducted by a psychiatrist or psychologist, quarterly community outpatient treatment progress reports, and copies of court orders were also included in these records. In many cases, the patient's course over the 5 years and status at 5-year follow-up could be obtained entirely from these records. When they could not, this information was obtained from the courts, from other parts of the criminal justice system, and from the patient's family.

RESULTS

The 79 subjects ranged in age from 22 to 71 years (median=33 years). Seventy (89%) were men and nine (11%) were women. Their educational levels ranged from third grade to 1 year of graduate school (median=4 years of high school). Other characteristics of the 5-year follow-up group are given in table 1.

The criminal charges of which the subjects had been found not guilty by reason of insanity are given in table 2. These charges were serious: 99% were felonies and 67% were crimes of violence against persons (table 2). Seventy-eight percent of the subjects had been arrested before: 58% for felonies, 20% for misdemeanors only, 33% for crimes against persons and property, 11% for crimes against persons only, and 34% for crimes against property only (table 1). Moreover, this was a seriously mentally ill, violent group: 72% had a history of psychiatric hospitalization, 97% had manifested Schneiderian first-rank psychotic symptoms at the time of the offense of which they were found not guilty by reason of insanity, 80% were diagnosed as having schizophrenic disorders, and 84% had committed acts of serious physical violence against persons, including the offense of which they were found not guilty by reason of insanity.

The median length of time from arrest to being found not guilty by reason of insanity was 6 months, and the median length of forensic hospitalization until the beginning of court-mandated community outpatient treatment was 20 months. (The median length of time from acceptance of these subjects into the program to their actually beginning community outpatient treatment was 5 months.)

TABLE 1. Characteristics of 79 Subjects in Court-Mandated Community Outpatient Treatment Who Had Been Found Not Guilty by Reason of Insanity

Characteristic	Number	Percent
Race		
White	39	49
Black	34	43
Hispanic	6	8
Marital status		
Married	8	10
Divorced or separated	27	34
Never been married	41	52
Widowed	3	4
Primary diagnosis		
Schizophrenic disorders	63	80
Schizoaffective disorders	3	4
Major affective disorders	7	9
Atypical psychosis	1	1
Atypical paranoid disorder	1	1
Phencyclidine (PCP) psychosis	1	1
Psychosis associated with organic brain syndrome	3	4
Living situation at time of arrest		
With parents	22	28
With spouse or girlfriend or boyfriend	18	23
With other relative	5	6
Board and care home	10	13
Boarding house	1	1
Alone in apartment	16	20
On the streets	5	6
Forest Service	1	1
Unknown	1	1
Source of support		
Employment	27	34
Parents	11	14
Spouse or girlfriend	4	5
Supplemental Security Income or Social Security disability insurance	25	32
Other forms of disability insurance	2	3
Aid to Families of Dependent Children	1	1
Veterans' Administration (VA) pension	7	9
No known source of support	2	3
History of psychiatric hospitalizations		
State hospital	38	48
Forensic mental hospitals	15	19
County, private, and VA hospitals and psychiatric wards of general hospitals	33	42
Previous arrests		
Felonies	46	58
Misdemeanors	16	20
None	17	22
Crimes against persons and property	26	33
Crimes against persons only	9	11
Crimes against property only	27	34
History of serious violence against persons[a]	66	84
History of residence in a board and care home	15	19
Held at least one job 6 months or longer	55	70

[a] From assault to murder, including offense of which found not guilty by reason of insanity.

The 79 subjects fell into three groups: 30 (38%) who were still in court-mandated community outpatient treatment at the 5-year follow-up date; 18 (23%) who had been released from court-mandated community outpatient treatment and freed from any further social control, either because they had been found "restored to sanity" or because their commitment time

TABLE 2. Criminal Charges of Which 79 Subjects in Court-Mandated Community Outpatient Treatment Were Found Not Guilty by Reason of Insanity

Charge	Still in Treatment (N=30)	Released From Treatment (N=18)	Release Revoked (N=31)	Total (N=79)
Violent crimes	25	8	20	53
First-degree murder	5	0	0	5
Attempted first-degree murder	0	0	1	1
Voluntary or involuntary manslaughter	3	1	0	4
Assault with intent to murder	1	0	2	3
Assault with a deadly weapon	5	6	10	21
Assault or assault with a deadly weapon on a peace officer	4	0	2	6
Assault to commit great bodily injury on a child	1	0	0	1
Armed robbery	4	1	4	9
Forcible rape	1	0	1	2
Shooting at an inhabited dwelling	1	0	0	1
Nonviolent crimes	5	10	11	26
Arson	2	2	4	8
Child molesting	1	1	2	4
Burglary	1	3	3	7
Grand theft auto	0	1	0	1
Felony vandalism	0	1	0	1
Possession of a firearm by a felon	0	0	1	1
Reckless driving with injury	1	1	0	2
Forged license	0	0	1	1
Malicious mischief[a]	0	1	0	1

[a] This is a misdemeanor rather than a felony.

had expired; and 31 (39%) whose release to court-mandated community treatment had been revoked and who never returned to such treatment during the 5-year follow-up period. It should be noted that the release of seven subjects had been revoked but they had later returned to court-mandated community outpatient treatment; at the 5-year follow-up date, three of the seven were still in court-mandated community outpatient treatment and four had been released from community outpatient treatment. Counting these seven subjects, we found that an unduplicated total of 38 (48%) of the 79 subjects who entered court-mandated community outpatient treatment had their conditional release revoked at least once during the 5-year follow-up period.

Rearrests and Hospitalizations

Twenty-five (32%) of the 79 subjects were rearrested at least once during the 5-year follow-up period, 18 (72%) of these for crimes of violence against persons. Thirty-seven (47%) of the 79 subjects were hospitalized in nonforensic hospitals at least once during the 5-year follow-up period. It should be noted that the median total length of time spent in the community was 46 months during the 5-year follow-up period. This is the sum of the time spent in court-mandated community outpatient treatment plus either the time from release from such treatment to the 5-year follow-up date or, for those whose release to community treatment had been revoked and who were later released from the psychiatric hospital, the time from that release until the 5-year follow-up date.

The median length of time that the subjects spent in court-mandated community outpatient treatment itself (within the 5-year follow-up period) was 33 months. During that period, 13 (16%) of the 79 subjects were rearrested—10 (13%) for violent crimes—and 27 (34%) were hospitalized at least once in nonforensic psychiatric hospitals (this does not include hospitalizations that led directly to revocation).

The highest total rearrest rate during the 5-year follow-up period was found in the 31 subjects whose release to court-mandated community treatment had been revoked and who never returned to such treatment: 15 (48%) of these patients were rearrested. Their median length of stay in court-mandated community outpatient treatment was only 14 months. The lowest total rearrest rate was found in the 30 subjects who were still in court-mandated community outpatient treatment at the 5-year follow-up date; only four (13%) of these subjects had been arrested during a median length of time of 53 months.

The highest total hospitalization rate (in nonforensic hospitals) during the 5-year follow-up period was again found in the 31 subjects whose release to court-mandated community treatment had been revoked and who never returned to such treatment: 17 (55%) had been so hospitalized. The 30 subjects who were still in court-mandated community outpatient treatment at the 5-year follow-up date had the lowest total hospitalization rate: 37% (N=11).

Significantly more of the 18 subjects released from court-mandated community outpatient treatment (N=10, 56%) had been found not guilty by reason of insanity of nonviolent crimes ($\chi^2=6.36$, df=1, $p<0.02$) (table 2). No one in this group was rearrested during court-mandated community outpatient treatment.

Outcome 5 Years After Referral

Table 3 gives the living situation of the subjects at the end of the 5-year follow-up period (5 years after referral to court-mandated community outpatient treatment). We considered being in a forensic hospital, in jail, in state prison, absent without official leave from community outpatient treatment, or living on the streets unsuccessful outcomes. There was a striking finding with regard to those whose release from court-mandated community outpatient treatment had been revoked and who never returned to such treatment.

TABLE 3. Living Situation 5 Years After Referral to Court-Mandated Community Treatment of 79 Subjects Found Not Guilty by Reason of Insanity

Living Situation	Still in Treatment (N=30)	Released From Treatment (N=18)	Release Revoked (N=31)	Total (N=79)
With family	3	7	3	13
With spouse or girlfriend or boyfriend	3	4	0	7
With roommate	1	1	0	2
Alone in apartment or hotel	9	2	1	12
Board and care home	9	2	1	12
Residential treatment center	3	0	0	3
Locked community facility	0	2	0	2
Room in private home	2	0	0	2
Forensic hospital[a]	0	0	12	12
Jail[a]	0	0	3	3
State prison[a]	0	0	5	5
Absent without leave from community outpatient facility[a]	0	0	3	3
On the streets[a]	0	0	2	2
Whereabouts unknown	0	0	1	1

[a] Unsuccessful outcomes.

Leaving aside the one subject whose whereabouts was unknown, we found that 25 (83%) of the remaining 30 subjects in this group had unsuccessful outcomes by the 5-year follow-up date, compared with none of the subjects in the other two groups ($\chi^2=58.87$, df=1, $p<0.001$).

DISCUSSION

This was a 5-year follow-up study of persons found not guilty by reason of insanity who were consecutively referred to and accepted for court-mandated community outpatient treatment as provided under California's Conditional Release Program for the Judicially Committed. Our findings support previous findings (8) that the typical person found not guilty by reason of insanity has a schizophrenic disorder and extensive experience with both the criminal justice and mental health systems.

The median length of hospitalization from commitment to the beginning of court-mandated community outpatient treatment was 20 months. Before that, the median length of time in jail from arrest to commitment was 6 months. Thus, those who entered court-mandated community outpatient treatment had had a median total length of detention of 26 months. The subjects in our study, then, had not been precipitously thrust out into the community.

Thirty-two percent were rearrested at least once during the 5-year period, and 72% of these arrests were for violent crimes; 47% were hospitalized in nonforensic hospitals at least once. Thus, this program is not without risks even though these subjects had been in a mandatory and structured program in the community. Generally, there was little reluctance to revoke the conditional release status of these subjects when indicated; indeed, the release of 48% of the subjects was revoked at least once during the 5-year period. It helps to put these outcomes in context to note that the median total length of time these subjects spent in the community was 46 months during this 5-year follow-up period.

The subjects who were still in court-mandated community outpatient treatment at the 5-year follow-up date had the lowest rearrest rate (13%) and the lowest hospitalization rate (37%). This is not surprising because arrests and hospitalizations frequently lead to revocation of the release to court-ordered community outpatient treatment. Moreover, even though these subjects were in the community for a median length of time of more than 4 years (53 months), they remained in structured community treatment during all of that time. In addition, the fact that they were still in court-mandated community outpatient treatment and not released can be viewed in itself as an indication that they needed this support and supervision and generally received them.

The group of greatest concern were the subjects whose release to court-mandated community outpatient treatment had been revoked and who never returned to such treatment. These subjects had a rearrest rate of 48% and a hospitalization rate of 55%. Their median length of stay in court-mandated community outpatient treatment was only 14 months. This group also had a strikingly higher proportion of unsuccessful outcomes as indicated by their status at the 5-year follow-up date: 81% were in a forensic hospital, in jail or state prison, absent without official leave from community outpatient treatment, or living on the streets.

Our data do not show if some, or any, of these unsuccessful outcomes could have been reversed by different management in court-mandated community outpatient treatment or if the unsuccessful outcomes were primarily related to the psychopathology and antisocial tendencies of these subjects. In any event, we looked at these cases in detail and speculated about what could have been done differently. It was our clinical impression that 11 of these 31 subjects had received insufficient supervision and structure. This is illustrated by the following two cases:

Case 1. Mr. A, a 40-year-old divorced man, was found not guilty of murder by reason of insanity. He had had multiple psychiatric hospitalizations and had been arrested three times in the past 4 years for assault with a deadly weapon. He was living with his girlfriend when the offense of which he was found not guilty occurred. Mr. A shot and killed his girlfriend when he heard voices telling him she had been unfaithful and was going to leave him. He was diagnosed as having schizophrenia, paranoid type.

Mr. A began court-mandated community outpatient treatment after 3 years of forensic hospitalization. He was hospitalized briefly on three occasions while in community outpatient treatment for being uncontrollable, demonstrating destructive and psychotic behavior, and refusing medication. Throughout his community treatment as an outpatient the staff noted that he consistently experienced depression and psychotic decompensation and was resistant to medications. He lived in a board and care home where he remained isolated; he was unable to tolerate any stress and would become bizarre and hostile. Despite this extremely poor level of functioning, he remained in court-mandated community outpatient treatment for 3½ years until his release was revoked and he returned to a forensic hospital, where he remained at 5-year follow-up. Just before his release was revoked, he had been given a "drug holiday," decompensated to the point of florid psychosis, and asked to be hospitalized. In court-mandated community outpatient treatment, he was seriously disturbed and experienced psychotic symptoms for which there was almost no effective intervention.

Given Mr. A's mental condition and his history of committing murder while psychotic, we think that a more structured community living situation than a board and care home and probably administration of intramuscular neuroleptic medications were indicated early in community outpatient treatment.

Case 2. Mr. B, a 37-year-old single man, was found not guilty of armed robbery by reason of insanity. He was arrested when he went into a restaurant, demanded food, and would not pay for it despite having money. He believed the waitress had something against him and fired a rifle at her but missed. He was diagnosed as having schizophrenia, chronic undifferentiated type, and had a long history of psychiatric hospitalizations, outpatient treatment, and medication. He had been arrested twice before for illegal possession of a firearm. He had lived in several board and care facilities, where he had struck staff and threatened residents.

Mr. B began court-mandated community outpatient treatment after 15 months of forensic hospitalization. Within 2 months, he began decompensating and threatening residents at his board and care home. He received individual "insight-oriented therapy focusing on his self-esteem and psychotic thinking." He was also given medication but took it sporadically. He remained consistently psychotic and depressed but was not hospitalized, and his release was not revoked. Approximately 2 years after his admission to community outpatient treatment, he was finally hospitalized for a brief period and then returned to community outpatient treatment. Shortly thereafter, he left treatment without having been discharged and was found in another state. He was returned to California, his release was revoked, and he was readmitted to the forensic hospital. A year later, he was discharged as having served his term of commitment. Several months later he was arrested for assault with a deadly weapon and sent to state prison, where he remained at 5-year follow-up.

It appears that this patient's severe mental disturbance was tolerated by the community outpatient treatment staff despite his history of serious violence. There was little if any work with him on impulse control and medication compliance. In addition, structure was not provided in his daytime activities and living situation. Court-mandated community outpatient treatment seems to have had no substantial therapeutic impact on him when, in our opinion, it might well have done so.

Still other problems were identified in the subjects whose releases were revoked and who never returned to court-mandated community outpatient treatment. One patient who had been doing well decompensated shortly after experiencing, in less than 1 month, both a change of therapist and the closing of the board and care home where he had been living. This example demonstrates the importance of continuity of care.

With regard to the 18 patients who had been released from court-mandated community outpatient treatment, it is not surprising that significantly more of these subjects had been found not guilty of nonviolent crimes by reason of insanity. Moreover, none of these subjects was rearrested during community outpatient treatment. Both the court and the community outpatient treatment staff would have less concern about releasing such persons from community outpatient treatment and social control than they would about persons found not guilty of violent crimes by reason of insanity or those who were arrested again during court-mandated community outpatient treatment.

The median length of time from acceptance to actually beginning court-mandated community outpatient treatment was 5 months. This period of time in the hospital before release into the community gave the hospital staff time to observe the patients' reactions to the prospect of moving to a less structured treatment setting. In a number of cases, problems such as decompensation, drinking, or assaultiveness occurred in a patient after his or her acceptance for court-mandated community outpatient treatment. This indicated a lack of readiness for community outpatient treatment; release was then delayed or cancelled and the patient was referred again at a later date. Delaying release appeared to be a valuable clinical practice. In cases where patients were referred for court-mandated community outpatient treatment but this recommendation was then rejected by the community outpatient treatment staff, the staff was very specific as to why the patient was being rejected, what behaviors needed to be changed, and what was generally expected of the patient before he or she could be accepted. Community outpatient treatment staff believe this contributes to more appropriate repeated referrals from the hospital.

CONCLUSIONS

The persons found not guilty by reason of insanity in this study had been referred and accepted for court-mandated community outpatient treatment. The subjects proved to be a severely mentally ill and dangerous group (97% had manifested first-rank Schneiderian psychotic symptoms at the time of the offense and 84% had committed acts of physical violence against persons). The subjects had spent more than 2 years in locked facilities (median of 6 months in jail plus 20 months in a forensic hospital). During the 5-year follow-up period, 32% were rearrested, 47% were hospitalized, and 48% had their conditional release status revoked. Thus, this program is not without risks even though these subjects had been in a mandatory and structured program in the community and there was in most cases little reluctance to revoke the release of these subjects when indicated.

Generally, persons who have been found not guilty of crimes by reason of insanity are difficult to treat in the community. We believe that these persons need social controls and treatment for relatively long periods of time if they are to adjust well in the community and simultaneously for the protection of society.

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Types of Patients Served by Various Providers of Outpatient Care in CMHCs

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Representative community mental health center (CMHC) survey data showed that psychiatrists differed from other CMHC providers of mental health services by serving the more seriously impaired patients who are admitted and readmitted to outpatient services. Psychiatrists also shared more outpatients with providers from other disciplines than providers in other disciplines shared with one another. The results are consistent with previous research on differences between disciplines and with the flight of psychiatrists from CMHCs but cast doubt on the hypothesis that psychiatrists see sicker patients than psychologists see because of differences in reimbursement between the two disciplines.

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Mental health services have always been manpower intensive. This manpower intensiveness has increased considerably, however, as delivery of mental health services has shifted from state hospital custodial care to outpatient care in communities. Professionals with specialized knowledge of therapies have become more important; the numbers of workers in the four core mental health service professions (psychiatry, psychology, social work, and nursing) have increased sharply during the last two decades (1).

During this time the community mental health center (CMHC) program, with its emphases on comprehensiveness, accessibility, continuity, equity, and patient participation in services, introduced special concerns about staff functioning. Would staff members cooperate through team functioning, communication, and use of community caregivers to meet patients' individualized needs for comprehensive and continuous care? Would staff members adapt their middle-class and professionally specialized attitudes to deal with problems of lower-class patients in community settings (2)? Would the treatment milieu be more therapeutic and less stigmatizing for patients if differences between the roles of staff and patients were blurred (3)?

This paper reports the most complete statistics available on differences in types of patients served by staff members of different disciplines in federally funded CMHCs. Although federal regulation of the CMHC program ended in 1980, some program features remain a model for community-oriented services, and CMHC functioning under the federal program is a baseline for evaluating community services under subsequent state and private sector leadership.

Our study tested several hypotheses concerning differences in the clientele of care-providing disciplines. Taube et al. (4) found that in office-based practice, psychiatrists' patients were "significantly more impaired than psychologists' patients," more likely to be over 55 years of age, more likely to have Medicaid coverage, less likely to be college educated, and less likely to be employed. They hypothesized that these differences in clientele were associated with differences in reimbursement of psychiatrists and psychologists and proposed that further research examine caseloads under conditions of comparable reimbursement structures. However, Knesper et al. (5) and Flaskerud (6) also found that psychiatrists' patients had higher proportions of severe mental problems than the patients of other providers in a variety of settings. Although these studies differed in their measures of impairment and their definitions of types of facilities, they supported the findings of Taube et al. while casting doubt on the differential reimbursement interpretation.

The present study tested the differential reimbursement hypothesis more thoroughly by examining caseloads in organized facilities (CMHCs) where the choice of providers for particular patients does not depend directly on third-party payments.

METHOD

Between July 1981 and June 1982, the National Institute of Mental Health (NIMH) surveyed patient additions (i.e., admissions and readmissions) to a representative sample of 48 federally assisted CMHCs in the United States. Sample CMHCs were chosen

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through a "controlled selection" process (7) that balances a sample across a number of variables simultaneously; the stratification variables selected were the center's size, length of time in operation, geographic region, and structure for providing inpatient service. CMHCs were asked for background data on all additions during the year and, for additions during October through December 1981, data about the services patients received for 3-6 months after admission. Since length of follow-up showed only minor differences, it is ignored in this report. Data on the disciplines of staff members who provided outpatient services (including intake, diagnostic evaluation, and medication) to particular patients were collected. Forty CMHCs provided data on services, and 36 provided information on providers' disciplines. The distribution of these 36 CMHCs over the four stratification variables was similar to that of the total sample of 48 CMHCs (although it somewhat favored CMHCs that had been in operation for shorter periods of time); thus, these CMHCs were representative of CMHCs in general. Data on providers were reported for 11,690 patient additions: 2,105 were reported to have been served by psychiatrists, 3,976 by psychologists, 4,012 by social workers, 598 by registered nurses, 2,957 by other mental health professionals, and 1,031 by paraprofessionals. These groups, of course, overlapped. In addition, about 7% of the patient additions were reported to have no provider of services.

To represent the population of CMHC additions in 1981, sample data were weighted by the reciprocal of the probability of selection, with adjustment for CMHCs that did not report or that reported for part of the year, and a ratio adjustment to match the total additions reported by all 692 federally funded CMHCs for 1980. Data on all of the patient background variables analyzed in this report were provided for more than 78% of their patients by the 40 reporting CMHCs. Missing data were imputed by matching cases for which data were missing with cases for which data were available. Matching was done on CMHC background characteristics, patients' demographic characteristics, and the first service the patients received. To test whether the use of imputed rather than reported data influenced the results, we analyzed the relationship between type of provider and patients' diagnoses using both reported and imputed data. Very similar percentages and significance levels were obtained, indicating that the results were not influenced by our solution to underreporting.

Standard errors were calculated by means of the SESUDAAN program (8), which takes into account the "design effect" in complex sample surveys. That is, our sample of additions, although representative, was not a simple random sample. Special statistical procedures such as those contained in the SESUDAAN program are therefore needed to estimate standard errors accurately.

Since our study combined testing of specific hypotheses and exploration of nonhypothesized differences, we used two different procedures to test significance. For specific hypotheses (i.e., the differences described by Taube et al. [4]), we made one-tailed Z tests of differences between percentages and used the standard 0.05 level of significance for each variable tested (except for impairment, which we assessed with two variables and for which we therefore set the significance level at 0.025 in each test). For nonhypothesized differences, we compared by means of two-tailed Z tests extreme groups on continuous variables and selected reference groups to other groups on categorical variables. We used Z tests, which do not use degrees of freedom, rather than t tests because of our large number of cases; the fewest in any comparison was 755.

Since multiple comparisons produce many differences at the 0.05 level by chance, we followed Grove and Andreasen's (9) suggestion to test overall significance within domains of variables by using the Bonferroni inequality procedure to adjust the probability for the number of tests. This is done by dividing the traditional 0.05 significance level by the number of statistical tests performed. The result is the level that must be reached if an individual test is to be considered statistically significant. This correction makes it more difficult for a particular value to be considered significant and is therefore a conservative procedure. For variables that showed overall significance, we also identified differences significant at the traditional 0.05 level by individual tests.

RESULTS

Tests of Hypotheses

To test the differences between patients of psychiatrists and patients of psychologists that were reported by Taube et al. (4), we compared only the estimated 142,782 additions (based on 2,002 reported cases) served by a psychiatrist but no psychologist and the estimated 302,186 additions (based on 4,375 reported cases) served by a psychologist but no psychiatrist. We tested differences between these groups on two measures that approximate degree of impairment: diagnosis and prior inpatient care (see table 1). Taube et al.'s findings about impairment and age clearly applied to CMHC additions. The percentages of impaired and elderly patients served by psychiatrists were more than twice as high as those served by psychologists. Taube et al.'s finding that psychiatrists' patients were more likely to be covered by Medicaid was also confirmed, although the difference was less striking. Their finding that psychiatrists' patients were less likely to have some college education was not confirmed.

Patterns of Providers

The survey item on types of providers of outpatient service included six choices: psychiatrist, psychologist,

TABLE 1. Tests of Hypothesized Differences Between CMHC Patient Additions of Psychiatrists and of Psychologists

	Additions[a]					
	Patients Served by Psychiatrists but Not by Psychologists		Patients Served by Psychologists but Not by Psychiatrists			
Characteristics Hypothesized as Greater in Psychiatrists' Patients	%	SE	%	SE	Z	p (one-tailed)
More impaired						
Diagnosis of schizophrenia or other psychosis	17.5	1.9	5.0	0.8	6.07	<0.0001
Prior inpatient care	31.6	3.1	14.3	1.5	5.02	<0.0001
More than 55 years of age	13.1	1.1	5.2	0.7	5.88	<0.0001
Expected payment by Medicaid	14.1	2.7	9.0	1.5	1.66	<0.05
No college education	74.9	2.5	70.1	2.3	1.42	>0.05

[a]Admissions and readmissions.

TABLE 2. Estimated Percentages of CMHC Outpatient Additions Served by Providers From a Particular Discipline Only or From Other Disciplines as Well

	Additions[a]			
	Outpatients Served by This Type of Provider Only		Outpatients Served by Other Types of Providers as Well	
Provider of Outpatient Service	%	SE	%	SE
Psychiatrist	18.6	3.04	81.4[b]	3.04
Psychologist	62.4	4.01	37.6	4.01
Social worker	60.1	3.00	39.9	3.00
Registered nurse	35.9	4.70	64.1[c]	4.70
Other mental health professional	56.1	3.28	43.9	3.28
Paraprofessional	50.9	4.19	49.1[d]	4.19

[a]Admissions and readmissions.

[b]Psychiatrists significantly different from psychologists ($Z=8.71$, $p<0.0001$), social workers ($Z=9.72$, $p<0.0001$), registered nurses ($Z=3.09$, $p<0.01$), other mental health professionals ($Z=8.33$, $p<0.0001$), and paraprofessionals ($Z=6.24$, $p<0.0001$).

[c]Nurses significantly different from even the next most sharing group, paraprofessionals ($Z=2.38$, $p<0.05$).

[d]Paraprofessionals significantly different from psychologists ($Z=1.98$, $p<0.05$).

social worker, registered nurse, other mental health professional, and paraprofessional. A paraprofessional was a provider who did not have at least a B.S. or B.A. degree. On the basis of the survey results, the following statistics are estimates for all CMHCs in the United States. CMHC outpatients were most likely to be served by a social worker (percentage±SE of outpatients=34.0%±3.30%) or a psychologist (32.5%±2.66%). Service by an "other mental health professional" (24.6%±3.57%) was less likely. Less likely still was service by a psychiatrist (17.9%±1.76%). Service by a paraprofessional (8.7%±2.45%) or a registered nurse (5.0%±0.80%) was relatively unlikely.

Providers in the various disciplines differed in how much they shared patients. As shown in table 2, psychiatrists shared more patients with members of other disciplines than did providers in any other discipline. Next were registered nurses, who shared significantly more patients than even the next most frequently sharing group, the paraprofessionals. Paraprofessionals did not differ significantly in sharing from the "other mental health professionals" or social workers but did share significantly more than did psychologists. Psychologists, social workers, and "other mental health professionals" did not differ significantly in sharing patients.

CMHC outpatients were most likely to receive all their outpatient services from providers in only one discipline (64%); 21% had two types of providers, 5% had three or more, and an estimated 9% had no record of any provider. Many of the patients with no recorded provider had received only intake or diagnostic service. Only six of the 15 possible combinations of two providers had more than 1% of the outpatient service cases. For almost half of the patients served by providers from two disciplines, a psychiatrist was one of the pair.

Clinical Characteristics of Patients

Admission diagnosis. The diagnoses of the patients were grouped into the 13 broad categories used by NIMH to summarize data reported by facilities (10). The percentages of patients in each diagnostic category who had various patterns of providers of outpatient service are shown in table 3. For this analysis, deferred diagnoses were considered to be missing data and were imputed. Among the multitude of possible comparisons, we chose to test the diagnostic category of schizophrenia and related disorders against other diagnostic groups. Schizophrenic patients are an especially relevant reference group because of the controversy over how well CMHCs serve the seriously mentally ill (11, 12). Even limiting our tests to comparisons with this one diagnosis, there were 120 tests (10 provider groups and 12 other diagnostic groups), requiring a corrected significance level of 0.0004. We indicate in table 3 the values that reached the 0.0004 (corrected) level of significance and those values that reached the 0.05 (uncorrected) level, to allow our readers to interpret the results using two levels of conservatism.

Summarizing on the basis of differences significant at the 0.05 level, schizophrenic outpatient additions were more likely to have psychiatrists involved in their

TABLE 3. Estimated Percentage Distribution of Providers of Services Among CMHC Outpatient Additions With Particular Admission Diagnoses

	Estimated Percentage of Outpatient Additions[a]					
Provider of Outpatient Service	Total (estimated N=1,084,000)	Schizophrenia (estimated N=85,000)	Mental Retardation (estimated N=20,000)	Alcohol-Related Disorders (estimated N=104,000)	Substance-Related Disorders (estimated N=56,000)	Organic Disorders (estimated N=24,000)
Psychiatrist only	3.3	6.1	7.0	2.5[b]	2.0[b]	4.1
Psychologist only	20.3	11.1	27.9[b]	14.6	21.8[b]	8.0
Social worker only	20.5	16.2	18.0	15.6	12.9	13.7
Registered nurse only	1.8	2.6	0.8[b]	1.2	0.4[b]	6.8[b]
Other mental health professional only	13.8	10.6	10.3	24.1[b]	24.4[c]	9.5
Paraprofessional only	4.4	3.2	4.8	5.6	5.4	6.1
Pair including psychiatrist	10.5	19.5	8.8[b]	7.3[b]	8.3[b]	11.7
Pair not including psychiatrist	10.8	7.8	9.6	10.7	13.9[b]	3.5[b]
Three or more	5.1	8.7	1.8[c]	5.6	5.7	3.9[b]
None	9.4	14.3	10.8	12.9	5.1[b]	32.6

[a] Admissions and readmissions.

[b] Value differs significantly ($p<0.05$) from the value for schizophrenic patients for the same type of provider (e.g., the 2.5% of patients with alcohol-related disorders who were served only by psychiatrists differed significantly from the 6.1% of patients with schizophrenia who were so served.

[c] Value differs significantly at the 0.05 level from that for patients with schizophrenia even considering the multiple tests (i.e., $p<0.0004$).

treatment (alone or paired with another provider) than additions in eight of the other 12 diagnostic categories. Schizophrenic additions were less likely to have psychologist providers only than additions in eight of the remaining 12 categories.

Schizophrenic additions were more likely to have registered nurses as their only providers than were additions with diagnoses in four other categories, but they were less likely to have registered nurses as their only providers than were those diagnosed as having an organic brain disorder. Service by two providers, neither of whom was a psychiatrist, showed a mixed picture that was the opposite of the one for nurses; that is, they were less likely to serve schizophrenic patients than patients in several other diagnostic categories but more likely to serve schizophrenic patients than persons with organic brain disorders.

Schizophrenic additions were less likely than additions with diagnoses of alcohol- or substance-related disorders to be served by "other mental health professionals." Schizophrenic additions were more likely to be served by three or more types of providers than were additions within seven of the 12 other diagnostic categories.

Prior care. Prior care is a measure of problem chronicity and—when the modality of care that has been received is considered—the restrictiveness of previous care. Patients' prior care experiences were ordered by restrictiveness of care from 1) no prior care to 2) prior outpatient care but no inpatient care to 3) prior inpatient care. Comparisons among the three levels of prior care for 10 patterns of providers entailed 30 tests, requiring a corrected significance level of 0.0017 to reflect a 0.05 level overall.

There were no significant differences between the provider patterns for patients who had had no prior care and for those who had had prior outpatient care only. However, patients with prior inpatient care were more likely than those with no prior care to be served by psychiatrists only ($Z=2.30$, $p<0.05$), by pairs of providers that included a psychiatrist ($Z=2.92$, $p<0.01$), and by three or more provider disciplines ($Z=2.25$, $p<0.05$); they were less likely to be served by psychologists only ($Z=2.12$, $p<0.05$). The provider patterns for patients who had had prior outpatient care but not inpatient care were between those of the other two groups.

Referral source. The most common referral source (i.e., self, family, or friend) was used as a standard for comparisons. This involved 80 tests, necessitating a corrected significance level of 0.0006 to reflect a 0.05 level overall. None of the comparisons reached this level of significance, and only 10 of the 80 comparisons reached the 0.05 level. Patients referred from state mental hospitals were more likely ($Z=3.32$, $p<0.001$) to see pairs of providers that included a psychiatrist and they were less likely to see psychologists only ($Z=2.66$, $p<0.01$) or social workers only ($Z=2.87$, $p<0.01$). Patients referred from private mental health professionals also were relatively likely to see pairs of providers that included a psychiatrist ($Z=2.69$, $p<0.01$) and they were unlikely to see social workers only ($Z=3.10$, $p<0.01$), but they were also unlikely to see mental health professionals who were not in the four core disciplines ($Z=3.30$, $p<0.001$). Patients referred from schools were most likely to see psychologists only ($Z=3.19$, $p<0.01$) and they were unlikely to see professionals who were not in the core disciplines ($Z=2.74$, $p<0.01$).

TABLE 3. Continued

Estimated Percentage of Outpatient Additions[a]							
Affective Disorders (estimated N=148,000)	Other Psychotic Disorders (estimated N=12,000)	Anxiety/ Somatoform/ Dissociative Disorders (estimated N=59,000)	Personality Disorders (estimated N=58,000)	Preadult Disorders (estimated N=57,000)	Other Non-psychotic Disorders (estimated N=243,000)	Social Mal-adjustment (estimated N=196,000)	No Mental Disorder (estimate N=23,000)
5.9	6.4	2.9	1.6[b]	4.8	2.5[b]	1.7[b]	3.7
15.8	10.2	17.8[b]	20.1[b]	29.1[c]	21.8[b]	27.0[c]	30.0[b]
17.9	10.7	20.3	24.1	19.9	26.1[a]	23.6	14.5
2.2	0.7[b]	5.1	1.6	2.2	1.6	0.6[c]	1.8
10.8	11.2	11.1	12.8	10.3	13.6	12.0	16.3
3.5	2.1	5.6	3.1	2.1	3.4	6.9	2.0
17.6	21.2	12.4	9.6[b]	7.5[b]	10.1[b]	4.4[c]	8.8[b]
11.9[b]	10.0	10.4	9.3	13.6[b]	10.4	12.1	9.8
6.4	10.2	4.0[b]	5.5	4.6[b]	5.1[b]	2.9[c]	1.7[c]
8.0	17.4	10.4	12.4	5.8	5.6[b]	8.8	11.4

Demographic Characteristics of Patients

The linear relationship of patient's age to type of service provider was explored by comparing the statistics for the age groups of 0–17 years and over 65 years for each of the 10 combinations of providers. With 10 comparisons, the corrected significance level was 0.005. Only the difference for psychologists as the only providers was significant at this level: psychologists served a much higher proportion of the young than of the elderly ($Z=4.37$, $p<0.0001$, two-tailed test). At an uncorrected confidence level, psychiatrists who were the only providers and pairs of providers in which one was a psychiatrist served a lower proportion of the young than of those over age 65 ($Z=2.42$, $p<0.05$, and $Z=2.87$, $p<0.01$, respectively).

Black additions differed significantly from white additions on only two of the 10 patterns of providers when the uncorrected 0.05 two-tailed test of individual differences was used. Blacks were less likely to receive outpatient services from psychologists only ($Z=2.58$, $p<0.01$), but were more likely to be served by providers from two disciplines including a psychiatrist ($Z=2.70$, $p<0.01$). No difference was significant when corrected for multiple tests. Hispanics differed significantly from whites in only one respect. They were less likely to be served by psychiatrists only ($Z=2.11$, $p<0.05$). The other ethnic groups did not differ significantly from whites in any comparison.

Only a few of the multiple comparisons for provider combinations across marital status groups or between the extremes of the educational groups had differences that reached the 0.05 level, and none of these comparisons reached the corrected level of 0.01.

The patient's expected source of payment at admission was used as a substitute for the patient's socioeconomic status. Nine categories of sources of payment were distinguished. The reference group we used to test differences was patients whose fees were discounted, the largest category of patients who received outpatient services (34%). There was no pattern in the few differences we found.

DISCUSSION

Our discussion focuses on two issues: the roles of the various mental health care disciplines in CMHCs compared with office-based practice and the implications of psychiatrists' role in CMHCs for CMHCs' recruitment and retention of psychiatrists.

Psychiatrists in CMHCs differed considerably from providers in other disciplines in how often they combined with providers in other disciplines to serve outpatients. They also differed from workers in other disciplines by serving a higher proportion of aged than young patients; of schizophrenic patients than those with alcohol- or substance-related disorders, personality disorders, other nonpsychotic disorders, or social maladjustment; and of patients who had had prior inpatient care than those who had had no prior care. This pattern suggests that psychiatrists in CMHCs serve a relatively higher proportion of the more severely disturbed patients, as Taube et al. (4) found in office-based practice and as Knesper et al. (5) found in a variety of settings.

Comparison of the present study with that of Taube et al. is limited by differences in reporting method, definitions of "psychologists" (e.g., in private practice more have doctorates), clientele, and amounts of service per patient, as well as the difference in reimbursement mechanisms. The last difference, however, makes our findings especially interesting. Taube et al. postulated that differences in clientele between psychiatrists and psychologists were due in large part to differences in their reimbursement mechanisms. In CMHCs, however, there is no individual reimbursement for seeing particular patients; thus, differences in reimbursement cannot explain the differing roles among providers. A better explanation for these differences is that psychiatrists are called on to provide services for which they are specially qualified, for example, evaluating and monitoring patients for medication and making differential diagnoses. Since these services may be more common for severely impaired patients, psychiatrists would serve such a clientele disproportionately and would be likely to combine with members of other disciplines to serve particular patients. Even in the Taube et al. study, there may have been several reasons for differences among disciplines. Surely Taube et al. were correct in stating that in office-based practice there are reimbursement-driven influences that differentiate the practice patterns of the various mental health disciplines, but there may be other influences, such as practitioner training and orientation. At least within CMHCs, economic factors do not seem to play a large role in differentiating provider patterns. It is likely that various factors, differently weighted, shape providers' roles in various settings.

Although we lack data on the issue, our findings suggest that the psychiatrists' role in CMHCs may affect the recruitment and retention of psychiatrists. The tendency for psychiatrists to see relatively high proportions of severely impaired patients may be problematic if it leads to their being involved with only a narrow range of patients and therefore not fully using their knowledge and skills. For example, psychotherapy-oriented psychiatrists may be willing to see severely ill patients but may want the opportunity to see some patients for psychotherapy. This problem may be exacerbated if some CMHCs, for efficiency, focus the psychiatrists' role very narrowly (e.g., restricting them to simply writing prescriptions). Severe role limitation makes the professional function as a technician and leads to job dissatisfaction.

Similarly, sharing patients with members of other disciplines may reduce psychiatrists' personal gratification in clinical work in CMHCs if this sharing is not truly teamwork. Many professionals enjoy working with other staff members and prefer an organized setting so that they have this opportunity. However, if the teamwork consists of a line of staff members at the psychiatrist's door with requests for a 2-minute consultation and a prescription, psychiatrists may find the work unrewarding.

Job satisfaction is important in light of growing evidence (13) that the proportion of psychiatrists working in CMHCs and other mental health facilities fell in the late 1970s. This decrease was undoubtedly due to many factors in addition to the types of patients and responsibilities assigned to psychiatrists, including a perception that CMHCs pay relatively poorly (14). However, since CMHCs served higher proportions of chronically mentally ill patients in the 1980s (15) and the numbers of psychiatrists decreased, especially in non-hospital-based CMHCs, the burden on the psychiatrists that remain in CMHCs has probably increased. With this increased burden of severely ill patients may have come a still further decrease in the scope of the psychiatrists' role (and therefore satisfaction) in CMHCs.

Langsley (11) suggested that CMHCs should become totally nonmedical. This may happen in some CMHCs by default rather than by design, and our data point to possible reasons. It is important to study CMHCs and the roles of the psychiatrists within them in the mid-1980s to determine whether the attractiveness of CMHC positions has decreased further, with a continued decline in psychiatrist staffing.

In this study we were able to examine staff roles only superficially. Future research should study ways in which mental health care disciplines can most effectively work together to provide services, how staff members of different disciplines actually differ and collaborate in treatment activities, and the impacts of different patterns of staff functioning on patients and on staff job satisfaction and careers. Pressures on organizations to operate efficiently may structure jobs in ways that are more costly in the long run because of staff turnover and low morale. Better data about the impact of staff roles on work effectiveness and costs will help CMHCs use staff members more wisely and serve patients better.

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The Manfred S. Guttmacher Award

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Diagnostic Classification Through Content Analysis of Patients' Speech

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Speech samples from 71 patients in four diagnostic groups were analyzed by two quantitative methods of speech content analysis, the results of which were entered into a discriminant analysis to test whether patients could be accurately classified back into their appropriate diagnostic groups. These classifications were compared with classifications made by two psychiatrists, blind to the patients' diagnoses, who read transcripts of the speech samples. The results suggest that data from the systematic quantification of lexical choice can be used to classify patients into their respective diagnostic groups and that this classification compares favorably with that done by psychiatric raters.

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In a classic treatise, Reik (1) used Nietzsche's metaphor of "listening with the third ear" to characterize the psychiatrist's special skill in listening and inference. More specifically, Reik referred to the fact that the patient's way of speaking—including posture, tone of voice, and rate of speech—may "betray a great deal about a person" (1, p. 136), even though these cues may not "enter the [psychiatrist's] field of conscious observation." Even earlier, Freud (2) went so far as to recommend *gleichschwebend*, or "free-floating attention," a specific style of listening that permits the psychiatrist to be maximally receptive to this multiplicity of cues. With this style, the listener becomes immersed in the flow of the patient's speech and simply takes in many simultaneous impressions. The listener does not attempt to quantify or consciously evaluate what he or she is hearing, letting more global impressions emerge without recourse to any systematic analysis of the verbal production.

While such a procedure may indeed be useful at certain times, it may be made more reliable by systematic quantification of those less obtrusive aspects of verbal style which actually condition the clinician's impression. The purpose of this paper is to suggest that attention to one subtle but measurable dimension of verbal behavior—choice of words, or "lexical choice"—can promote increased reliability of inferences made from listening and result in improved differential diagnostic skills. "Lexicon" refers to a potentially available dictionary or vocabulary; "lexical choice" refers to the particular words used by a speaker to express a given thought. For example, a number of witnesses observing the same event (e.g., a driver making a sudden stop) might describe the scene using somewhat different words, such as, "He came to an abrupt halt," "He stopped dead in his tracks," and "He came to a screeching stop."

These variations in lexical choice (e.g., the figurative use of affectively loaded words, such as "dead" or "screeching") may convey a great deal about the speaker if they are repeatedly used in the course of an interview. Lexical choice clearly gives us cues about such characteristics as education and social class. Content analysis studies (3–5) have also suggested that vocabulary betrays aspects of affective state, interpersonal style, and psychopathology. In this paper, we attempt to demonstrate how lexical choice distinguishes several groups of patients from one another.

In this study, we collected samples of free speech from four groups of patients. We then compared the diagnostic accuracy attained by two quantitative methods of analyzing speech content in these samples with the diagnostic accuracy of two psychiatrists who read transcripts of the samples. One method of content analysis was the Gottschalk-Gleser schema (6), which requires a trained rater for scoring. The other method was the Dartmouth adaptation (3) of the computerized General Inquirer content analysis program and the Harvard Third Psychosociological Dictionary developed by Stone and associates (7).

The Gottschalk-Gleser approach to content analysis represents an attempt to incorporate some methods of clinical inference into a systematic method of content

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analysis. It is based on a psychodynamic view of language and also takes into account both the syntax of the clause and the semantics of the words; references can vary from a single word to a subject and object linkage across several clauses. In contrast, the General Inquirer/Harvard Third approach to content analysis is essentially one-dimensional; counts of single words are taken with no attempt to analyze syntactical or grammatical linkages. The assumption behind use of the Harvard Third dictionary is that choice of vocabulary—independent of the meaning of the sentence's deep structure—betrays the speaker's affect. For example, the sentences "He turned off the engine" and "He killed the engine" refer to precisely the same action, but in Stone et al.'s schema, the word "killed" implies both aggression and death. The Gottschalk-Gleser schema also registers the word "killed" as indicating hostility but modifies the cumulative count according to the nature of the persons showing and receiving the hostility.

Despite these differences, both of these approaches to content analysis involve the quantification of language and ignore the *DSM-III* criteria available and necessary to a clinical reader. Therefore, using data derived with these methods for the purpose of classifying four samples of patients, we were able to test the extent to which words chosen by individuals in each group yielded diagnostic information. By evaluating the classification performance of both these methods and of clinicians, we were asking, Given the same free associative (not diagnostic interview) information, how do systematized methods of quantifying speech compare with clinical judgment in terms of diagnostic accuracy? and How does a computerized and more purely lexically based system of content analysis (General Inquirer/Harvard Third) compare with one that has been widely used in psychiatric research (Gottschalk-Gleser)?

METHOD

Adding to speech samples from subjects used in earlier research (4, 5), we studied 71 subjects from four diagnostic groups: somatization disorder (N=17), paranoid disorders (N=25), cancer (N=17), and major depression (N=12). Details about the sources and diagnoses have been described previously (4, 5). Briefly, the somatization disorder group included patients referred to one of us (T.E.O.) who was working as a member of a family practice center. Subjects for the other three groups were selected from the inpatient and outpatient services of a general hospital, a Veterans' Administration medical center, and a state hospital. The 25 paranoid patients all had active paranoid delusions of at least 4 weeks' duration. The *DSM-III* diagnoses fulfilled by these patients were schizophrenia, paranoid type (N=9); paranoia (N=6); bipolar disorder, manic, with mood-incongruent psychotic features (N=5); and organic delusional syndrome (N=5). All the patients with somatization disorder and major depression fulfilled the respective *DSM-III* diagnostic criteria and had no evidence or history of psychotic features. The cancer patients had either lung or breast cancer and were undergoing chemotherapy or radiation therapy.

After obtaining informed consent, the interviewer introduced himself to the patient with the following statement:

> We're interested in how people seeing doctors feel about things and how they express themselves. We'd like you to talk for about 5 minutes about anything you like. So talk about anything—it could be about things at home with your family, or work, or school, or books, or the past, present, future, or anything. We don't care so much what you say but will be interested in the words you use to say it.

The interviewer spoke only when necessary to encourage the patient to continue speaking. This procedure is the standard speech collection method described previously for both the Gottschalk-Gleser system (6) and the Dartmouth adaptation of the General Inquirer/Harvard Third method (3). Of the 71 resulting samples of free speech, 62 were obtained by the same interviewer (T.E.O.). The other nine samples, all from depressed subjects, were obtained by a second-year medical student who was working as a research assistant.

Transcripts of the speech samples were sent for scoring to a senior investigator involved in the development of the Gottschalk-Gleser technique. This rater was blind to the subjects' diagnostic classifications. The transcripts were scored on the 12 most widely used and valuable of the Gottschalk-Gleser scales (8), i.e., the seven anxiety and five hostility scales: death anxiety, mutilation anxiety, separation anxiety, guilt anxiety, shame anxiety diffuse anxiety, total anxiety, overt hostility, covert hostility, total hostility, inward hostility, and ambivalent hostility. In scoring these scales, the categories are differentially weighted in proportion to their assumed intensity. For example, a direct statement, "I am anxious" or "I feel like killing Joe," is given a higher weight than an indirect reference, "I am not anxious" or "He disapproves of Joe." The weights were initially devised on the basis of psychoanalytic theory, but they were subsequently revised according to the results of empirical testing. The grammatical clause is the individual unit analyzed, and a correction factor is used to take into account the number of words in the scored communication.

The transcripts also were analyzed by the General Inquirer/Harvard Third method (7). The General Inquirer procedure reduces each word in a text to a base form before performing its dictionary-searching routine and, upon finding a match, adds increments to a counter for the category or categories to which the word has been assigned. Each word or stem is assigned to at least one, but sometimes two or more, of 83 categories. The word "ache," for example, is assigned to the distress category, whereas the word "trousers" is assigned to both the clothing and male theme categories. Ambiguous, unclassifiable words are also counted. A text is thus described by the proportion of words falling into each category relative to the total number of classified words.

A set of the transcripts was also given to a Fellow in consultation-liaison psychiatry and a fourth-year psychiatric resident. They were instructed to read the transcripts and, using any information in them, to assign each transcript to one, and only one, of the four identified diagnostic groups. The raters were not informed of the number of subjects in each of the four groups.

Each sample of speech provided at least 500 words (mean ± SD=822 ± 198). The statistical analysis consisted of three phases. For each method of content analysis, the procedure was as follows. First, a one-way analysis of variance (ANOVA) of diagnostic groups (somatization disorder, paranoid disorders, major depression, and cancer) was conducted for frequency data in each category. Second, predictor variables for stepwise discriminant analysis were selected from categories for which the test was significant at the $p<0.05$ level. Classification analysis was then performed on the basis of discriminant functions. Third, the classification performances of the two methods and the two psychiatrist judges were compared in a mixed ANOVA design, with diagnostic group as a between-subjects factor and method (Gottschalk-Gleser, General Inquirer/Harvard Third, psychiatrist 1, psychiatrist 2) as a within-subjects factor.

RESULTS

ANOVAs on data from the 12 scales of the Gottschalk-Gleser procedure showed that the groups differed significantly on six scales: hostility inward, shame anxiety, mutilation anxiety, total anxiety, separation anxiety, and diffuse anxiety (see table 1). Analyses of data from the 83 categories of the General Inquirer/Harvard Third procedure showed that the groups differed significantly on 19 categories (see table 1).

Data from the six statistically significant scales of the Gottschalk-Gleser procedure were entered into a stepwise discriminant analysis with the F values for entry and removal set at 1.5. Five of the six variables were selected in the analysis—all except total anxiety. Because a test of the equality of group covariance matrices indicated marked inequality (Box's M= 118.4, $p<0.001$), quadratic discrimination, which incorporates separate covariance matrices, was used for classification. The results of this classification procedure are presented in table 2. As can be seen by examining the table, the diagnostic categories of 62% of the subjects were correctly classified when the Gottschalk-Gleser procedure was used.

TABLE 1. Significant Differences in Speech Content Among Patients in Four Diagnostic Groups According to Two Systems of Content Analysis

	Analysis of Variance	
Category of Speech Content	F (df=3, 67)	p
Gottschalk-Gleser system		
Hostility inward	8.94	<0.001
Shame anxiety	4.19	<0.01
Mutilation anxiety	4.19	<0.05
Total anxiety	4.07	<0.05
Separation anxiety	3.65	<0.05
Diffuse anxiety	3.21	<0.05
General Inquirer/Harvard Third system		
Distress	12.46	<0.001
Lower status	5.64	<0.01
Sign weak	5.10	<0.01
Political	4.73	<0.01
Self	4.68	<0.01
Family	4.37	<0.01
Quantity reference	4.13	<0.01
Work	3.84	<0.05
Space reference	3.81	<0.05
Control	3.60	<0.05
Tool	3.59	<0.05
Defense mechanism	3.37	<0.05
Sign ascend	3.34	<0.05
Communicate	3.32	<0.05
Selves	3.16	<0.05
Recreational	3.14	<0.05
Sex theme	2.90	<0.05
Small group	2.81	<0.05
Equal	2.75	<0.05

Data from the 11 most statistically significant categories of the General Inquirer/Harvard Third procedure were entered into a stepwise discriminant analysis. These 11, rather than all 19 significant categories, were chosen in order to avert the possibility that the covariance matrix for the smallest diagnostic group (major depression, N=12) would be singular in the event that all variables were selected. The F value for removal was set at 1.5, but the F value for entry was raised to 2.0 to control for the probability of increased type I error, given the larger number of variables than in the analysis of the Gottschalk-Gleser data. Seven of the 11 variables were selected in the analysis: distress, lower status, work, self, political, sign ascend, and quantity reference. Quadratic discrimination was used for classification because the group covariance matrices were not equivalent (Box's M=181.21, $p<0.001$). The results in table 2 show that the diagnostic categories of 80% of the subjects were correctly classified by using the General Inquirer/Harvard Third method.

Table 2 also shows that the two psychiatrists together correctly classified an average of 66% of the subjects.

For a given subject, correct classification by a method was scored as 1 and incorrect classification was scored as 0. ANOVAs on these data showed significant differences between groups (F=6.6, df= 3, 67, $p<0.005$) and between methods (F=4.1, df= 3, 201, $p<0.01$). There also was a Group by Method interaction (F=2.2, df=9, 201, $p<0.05$), meaning that

TABLE 2. Correct Diagnostic Classification of 71 Patients by Two Systems of Speech Content Analysis and by Psychiatrists

		Patients Correctly Classified					
		Gottschalk-Gleser System		General Inquirer/Harvard Third System		Average of Two Psychiatrists' Ratings	
Diagnostic Group	N	N	%	N	%	N	%
Somatization disorder	17	8	47	17	100	10.0	59
Paranoid disorders	25	14	56	16	64	13.0	52
Cancer	17	16	94	14	82	14.5	85
Major depression	12	6	50	10	83	9.5	79
Total	71	44	62	57	80[a]	47.0	66

[a] Significant difference between the General Inquirer/Harvard Third and the Gottschalk-Gleser methods ($F=7.72$, $df=1, 67$, $p<0.01$) and between the General Inquirer/Harvard Third method and the psychiatrists' ratings ($F=4.52$, $df=1, 67$, $p<0.05$) (nonorthogonal planned comparisons).

the differences in results between methods were not equivalent across the four diagnostic groups. The Huynh-Feldt epsilon (9) for the tests involving the within-subjects factor was 1.0, indicating that these tests were not optimistically biased.

Nonorthogonal planned comparisons were performed to contrast the two methods of content analysis with each other and with the combined performance of the psychiatrists. As can be seen in table 2, the General Inquirer/Harvard Third method yielded more accurate classification than either the Gottschalk-Gleser method ($F=4.52$, $df=1, 67$, $p<0.01$) or the psychiatrists ($F=4.52$, $df=1, 67$, $p<0.05$). There was no difference between the Gottschalk-Gleser method and the psychiatrists ($F<1$). However, the superiority of the General Inquirer/Harvard Third method is qualified by the presence of the interaction effect. The General Inquirer/Harvard Third method was not more accurate than the other methods in identifying all of the diagnostic groups. For example, it is clear that the methods did not differ for the cancer group, where the General Inquirer/Harvard Third method had the lowest accuracy. Nevertheless, the General Inquirer/Harvard Third method yielded the most reliable classification overall.

DISCUSSION

The results of this study suggest that data from the systematic quantification of lexical choice can be used to classify patients into their respective diagnostic groups and that this classification compares quite favorably with that done by psychiatrist judges. The finding that the more purely lexical General Inquirer/Harvard Third system yielded a significantly better classification than did the Gottschalk-Gleser system suggests that lexical choice is a meaningful dimension of verbal behavior and, especially, that it is a potent reflector of a speaker's qualities. Content analysis can help us understand our intuitive insight into a speaker's characteristics by systematizing our often nonconscious observation of subtle codes such as those which are found in lexical choice.

The classificatory power of the General Inquirer/Harvard Third system suggests that cues about affective state, interpersonal stance, and character pathology are imbedded at the lexical level. While Reik pointed to speech rhythm and voice timbre as betrayers of internal states, our analysis implies that careful attention to word choice greatly enhances diagnostic and interpersonal sensitivity. Obviously, the frequency of words and themes is only one of many ways in which emotional and mental states are expressed. Although the richness and range of information communicated in this manner may be limited, it is apparently reliable.

The performance of the psychiatric raters in classifying the cancer and depressed patients must be interpreted in light of the fact that overt diagnostic statements were made by many of these subjects. Samples from 12 (71%) of the 17 cancer patients included statements about having cancer or cancer treatment, for example, "OK, my name is Anna and I have breast cancer, which I am sure is on its way out" and "I had had 20 treatments. Twenty cobalt treatments." Not surprisingly, then, the psychiatrists were able to correctly identify 85% of the cancer patients, which is comparable to the 94% and 82% by the Gottschalk-Gleser and the General Inquirer/Harvard Third systems, respectively. Similarly, samples from eight (67%) of the 12 depressed patients suggested fairly clearly some of the *DSM-III* criteria for major depression, as in the following: "This is the lowest I have ever been. I have never been so . . . , you know, depressed in my life. And you get up wondering, well, am I ever going to get better?" Thus, the psychiatrists were able to correctly classify 78% of the depressed sample, in comparison to the 50% and 83% correctly classified by the Gottschalk-Gleser and the General Inquirer/Harvard Third methods, respectively.

Our findings demonstrate that lexical content analysis may be superior to unstructured reading of transcripts by clinicians in cases where common diagnostic clues are not clearly conveyed. For example, in the somatization disorder group, 14 (82%) of the 17 transcripts contained infrequent somatic complaints (symptoms which, if present, would have been helpful to the psychiatric raters). Nevertheless, the General Inquirer/Harvard Third procedure was able to correctly classify 100% of the somatization disorder group. The following excerpt is an example from a somatization disorder patient who was classified as either depressed or paranoid by the two psychiatrist raters (Harvard Third categories in brackets after the words linked to them).

> I am AFRAID [distress] to do it. I am just like . . . , I am just AFRAID [distress] to let go because it, it just feels like that is . . . , it is like something is bothering me . . . and I am . . . I am really SCARED [distress]. . . . That SCARES [distress] me . . . and like with the KIDS [lower status], I do not know. . . . I mean one Mellaril is not going to . . . , I do not think one Mellaril is going to make the difference between sanity or insanity in anybody's life.

This passage demonstrates a high use of two categories of which the somatization disorder group had greater mean frequencies. In addition, the use of the word "kids" shows how content analysis makes use of the connotative aspect of words rather than relying on manifest meaning. In the General Inquirer/Harvard Third method, regardless of its specific contextual use, the individual word "kids" is classified as lower status, in contrast to higher status words such as "parents," "mother," or "father." This passage also contains information that a psychiatrist rater could use to misclassify this subject as psychotic, such as the phrase "the difference between sanity or insanity" and the mention of the antipsychotic drug Mellaril (thioridazine).

The results of this content analysis study suggest that in the absence of sufficient diagnostic clues, use of preconscious communication, as pointed to by Freud and Reik, may serve as an adequate alternative technique for differential diagnosis. Our results also suggest that clinicians may make diagnostic errors by relying on heavily connotative lexical items outside of a systematic interview or analysis. Thus, it may prove valuable for the clinician to analyze the speech content of a particular patient when diagnosis is difficult or ambiguous. This would permit identification of key words to listen for in the patient's discourse that might signal the presence of a certain disorder.

Before content analysis can be recommended for widespread use, several issues must be resolved. Although the reliability of content frequencies over time has been established (10), further work is underway to examine the effect on thematic content of the context and stimulus used in collecting the samples of speech.

At this point, we agree with others (11) that content analysis procedures can represent the basis for a hybrid form of objective/projective test, one that uses the advantages of both modalities. More immediately, we feel that content analysis can be viewed as a reminder, if not a means, to teach clinicians that there are supplemental ways of listening to patients, ways that can help us reliably identify diagnostic conditions in the absence of historical data and other forms of hard evidence.

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The Definition of a Psychiatrist: Eight Years Later

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In 1980, psychiatric practitioners and educators were surveyed to determine their concepts of the knowledge and skills that define a specialist in psychiatry. The authors repeated this survey, expanding the list of skill and knowledge items and asking respondents to comment on whether particular skills or knowledge were important to a psychiatric subspecialty. Less importance was ascribed in the current survey than in the earlier survey to certain long-term and social psychotherapies, and more importance was ascribed to descriptive or biological psychiatry; brief or supportive therapies; psychopharmacological agents; consultation-liaison psychiatry; evaluation of children, the aged, and alcoholics; and certain desirable personal characteristics of the psychiatrist.

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In 1982, one of us (D.G.L.) and Hollender (1) reported on a survey of psychiatric teachers and practitioners to determine what skills and knowledge define a specialist in psychiatry. The survey was conducted in 1980. The teachers were all members of the American Association of Chairmen of Departments of Psychiatry and the American Association of Directors of Psychiatric Residency Training. Of 430 teachers contacted, 299 (70%) responded. The practitioners represented a 1 in 50 random sample of members of APA who were not salaried academicians. Of 430 practitioners contacted, 183 (43%) responded. Thus, there were 482 respondents. The questionnaire consisted of 32 items regarding skill, 41 items regarding knowledge, and 12 describing attitudes. Analysis of the returns suggested that the respondents felt psychiatrists were clinicians whose principal skills were in evaluating and treating psychiatric disorders. The highly rated evaluative skills were the ability to interview, decide on the need for hospitalization, diagnose accurately, assess potential for suicide, consult in a general hospital, and conduct neurological and physical examinations. Highly rated treatment skills focused on a psychiatrist's ability to formulate a plan and carry it out. The attitudinal descriptors did not ultimately distinguish psychiatrists from other physicians because they were so general. They included such dimensions as ethical conduct, commitment to the maintenance of competence, and responsibility to patients.

Because considerable changes have occurred in the science and practice of psychiatry since 1980, we replicated the earlier study. Not only has there been a remarkable series of advances in the field of biological psychiatry, but new approaches to psychotherapy have been added to the knowledge base. Changes in third-party funding have influenced practice. We have been aware of diminishing support for long-term psychotherapy and increasing use of short-term and crisis-oriented psychotherapies. The fact that psychotherapy is being increasingly conducted by nonpsychiatrists (psychologists, social workers, and counselors, for example) has influenced the use of the psychiatrist's time; the "remedicalization" of psychiatry has proceeded rapidly. All of these factors suggest that psychiatrists practice in a different style than was common in 1980. These changes may have altered the earlier general agreement on the skills and knowledge that define a specialist in psychiatry as found in the 1980 survey.

METHOD

A questionnaire was constructed consisting of 48 items regarding skill and 51 items regarding knowledge. These included the 32 items regarding skill and the 41 items regarding knowledge used in the 1980 survey. Additional items were added as a result of consultation with knowledgeable colleagues. The questionnaire asked respondents to rate each skill or knowledge item as either definitely, probably, or probably not required in a competent general psychiatrist. The questionnaire also asked respondents to rate whether each type of knowledge or skill should be considered an important aspect of a psychiatric subspecialty. The debate about subspecialization and the need for established credentials for subspecialties prompted us to include this rating. We did not ask for definitions of specific subspecialties.

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The questionnaire was sent to the 130 members of the American Association of Chairmen of Departments of Psychiatry and the 355 members of the American Association of Directors of Psychiatric Residency Training. It was also sent to 499 practitioners. The names of practitioners were obtained from the computerized files of certified psychiatrists of the American Board of Medical Specialties. In those files a diplomate may indicate a practice pattern of being in full-time private practice or full-time hospital or clinic practice, full-time academic practice, or other types of practice. Only those who were in full-time hospital and/or clinic practice were selected for the survey. The sample represents approximately 1 in 50 of the certified psychiatrists in full-time hospital and/or clinic practice.

Of the 499 practitioners, 223 (45%) responded. This response rate was 2% greater than it was for practitioners in the 1980 survey (43%). Fifty-seven (44%) of the 130 chairmen and 200 (56%) of the 355 training directors responded. The response rate for these two groups of teachers was 53% (257 of 485), 17% less than it was for chairmen and training directors in 1980 (70%). The total 1987 response rate of 49% (480 of 984) compared well with the 1980 response rate of 56% (482 of 860), suggesting that the two sets of responses are from generally similar populations.

As in the 1980 study, the initial 1987 responses rating a skill or knowledge item as definitely or probably required were tabulated separately but doing so did not substantially change the rankings, so the ratings for definitely and probably required were combined. We then analyzed the degree of agreement between teachers and practitioners as to whether a skill or knowledge item was or was not required to define a specialist in psychiatry. This is the same type of analysis used in the 1980 study. The items were then ranked according to the degree of agreement between teachers and practitioners.

RESULTS

Tables 1 and 2 list the rankings and percent of agreement between teachers and practitioners for skill and knowledge items. The rank order from the 1980 study is also shown for purposes of comparison. In comparing ranks for 1980 and 1987, the reader should realize that there are differences in the numbers of items for both skills and knowledge. There were 32 skill items and 41 knowledge items in 1980, compared with 48 skill items and 51 knowledge items in 1987. A rank of 10 out of 41 is not the same as a rank of 10 out of 51. More than 50% of the respondents rated 45 of the 48 skill items in 1987. Sixteen skill items had an agreement rating of more than 90%. All 51 of the knowledge items received agreement ratings of more than 60%, and 20 of the 51 items had ratings of 90% or more. In 1980, 23 of 32 skill items received agreement ratings of more than 50% and 11 items had an agreement rating of more than 90%. Of the knowledge items in 1980, 38 of 41 had agreement ratings of more than 50%, and eight of the 41 received agreement ratings of more than 90%.

Skills

As in the 1980 study, the list of the skills agreed on by more than 50% of the respondents could be grouped under the categories of evaluation, treatment, personality of the psychiatrist, record keeping, and the ability to assess, treat, and/or manage certain conditions. Of the 25 highest ranked and most frequently listed items, eight—ranked 1, 3, 4, 6, 12, 14, 21, and 23—focused on evaluation, five—ranked 8, 11, 13, 15, 17—focused on treatment, six—ranked 2, 5, 7, 9, 16, and 18—focused on the personality of the psychiatrist, five—ranked 19, 20, 22, 24, and 25—focused on assessment, treatment, and/or management of certain conditions, and one—ranked 10—focused on record keeping.

Evaluation and treatment skills were ranked highest. The evaluation skills were among the highest ranked items, but in the 1987 study there was a substantial shift from the 1980 rankings. Items describing the personality of the psychiatrist achieved higher rankings in the 1987 study. The ability to recognize countertransference problems and personal idiosyncrasies moved from rank order 10 in 1980 to 2 in 1987. The ability to demonstrate interest, tact, and compassion moved from rank order 9 to 5.

Evaluation skills that dropped in ranking were of interest. The ability to formulate a problem list and a corresponding treatment plan and implement it through personal effort or appropriate referral dropped from rank order 5 to 17, the ability to evaluate children dropped from rank order 23 to 39, and forensic evaluation dropped from rank order 24 to 40.

Treatment skills continued to have high rankings, but in the 1987 survey, we included some that were not part of the 1980 study. Among these were the ability to do crisis intervention, which achieved a ranking of 11, and the ability to conduct brief psychotherapy, which was ranked 15. Supportive psychotherapy continued to be the highest ranked treatment skill at 8, and the ability to use psychopharmacological agents effectively was ranked 13, compared with 8 in 1980.

Treatment skills that achieved low rankings in 1987 were similar to those which were ranked low on the list in 1980. Examples are the use of hypnotic interviews, play therapy, behavior modification therapy, psychoanalytically oriented psychotherapy, treatment of a dying patient, and group psychotherapy. Proficiency in psychoanalytically oriented psychotherapy was ranked low in both 1980 and 1987. By contrast, supportive psychotherapy with awareness of psychodynamic issues, crisis intervention, and brief psychotherapy were ranked very high on the list as important skills.

TABLE 1. Agreement Between 223 Psychiatric Practitioners and 257 Psychiatric Department Chairmen and Training Directors on Skills Necessary in a Psychiatrist

Skill	1987 Agreement (%)	1987 Rank	1980 Rank
Conduct a comprehensive diagnostic interview	94.4	1	1
Recognize countertransference problems and personal idiosyncrasies as they influence interactions with patients and be able to deal with them constructively	93.9	2	10
Make accurate psychiatric diagnoses	93.7	3	4
Evaluate the need for hospitalization	93.3	4	2
Demonstrate consistent interest, tact, and compassion for the patient and family	93.1	5	9
Assess suicidal and homicidal potential or potential for assaultive behavior	92.9	6	6
Demonstrate the qualities of reliability, conscientiousness, and integrity	92.9	7	3
Provide supportive psychotherapy with awareness of psychodynamic issues	92.9	8	7
Remain objective, keeping a professional stance, yet not becoming either too distant or too involved	92.5	9	12
Maintain adequate records, including history, mental status, physical examination, diagnostic tests, and notes indicating the progress of treatment	92.3	10	11
Conduct crisis intervention	91.7	11	
Use appropriate laboratory tests, psychological testing, and other diagnostic procedures	91.4	12	14
Use psychopharmacological agents effectively	91.2	13	8
Construct a comprehensive assessment of the problems of a physically or psychosomatically ill patient referred for consultation and communicate it to the referring physician along with practical suggestions for management	90.6	14	13
Conduct brief psychotherapy	90.6	15	
Develop liaison relationships with nurses, physicians, and social workers	90.2	16	18
Formulate a problem list and a corresponding treatment plan and implement it through personal effort or appropriate referral	89.6	17	5
Work harmoniously as a member of a mental health team in information gathering, treatment planning, and implementation	88.5	18	16
Undertake the psychiatric treatment of a patient with psychophysiological or physical illness	88.3	19	19
Assess and treat and/or manage psychiatric problems of the aged[a]	87.9	20	
Assess developmental and psychopathological problems of adolescents[a]	87.5	21	
Assess and treat and/or manage alcoholism[a]	87.3	22	
Conduct a diagnostic family interview	86.7	23	17
Assess and treat and/or manage eating disorders	85.6	24	
Assess and treat and/or manage sedative and/or psychostimulant abuse	85.2	25	
Teach colleagues and students in medicine about knowledge and skills appropriate to psychiatry	83.3	26	21
Assess and treat and/or manage narcotics abuse[a]	78.7	27	
Conduct outpatient family or marital therapy	78.1	28	
Perform a competent physical examination, including a detailed neurological examination	78.1	29	20
Assess and treat and/or manage sexual dysfunction	77.3	30	
Conduct inpatient group psychotherapy	75.2	31	26
Administer a psychiatric treatment program (e.g., inpatient, outpatient)	74.4	32	
Conduct outpatient group psychotherapy	73.9	33	27
Conduct psychotherapy with adolescents[a]	73.7	34	
Conduct cognitive therapy	73.3	35	
Demonstrate proficiency in psychoanalytically oriented psychotherapy	73.1	36	22
Conduct a neurobehavioral assessment	70.4	37	
Conduct psychotherapeutic treatment of a dying patient	70.2	38	29
Conduct a thorough evaluation of children and their families in cases where a child is the identified patient[a]	68.7	39	23
Conduct forensic evaluation and give testimony on issues such as mental competency, sanity, and compensation for psychological or mental injury[a]	68.3	40	24
Comprehensively manage psychiatric problems of patients with epilepsy, brain injury, and other structural brain abnormalities	67.5	41	
Administer ECT	65.0	42	28
Conduct behavior modification therapy	61.0	43	30
Assess and treat and/or manage mental retardation[a]	58.9	44	
Conduct interventions appropriate to preventive psychiatry at the community level	57.3	45	
Conduct play therapy[a]	42.9	46	32
Conduct psychiatric research	41.2	47	
Use hypnotic interviews for diagnostic purposes	38.3	48	31

[a]More than 50% of each group considered this an important aspect of a psychiatric subspecialty.

Knowledge

Knowledge items paralleled the skill items in ratings for evaluation, treatment, and personality of the psychiatrist. The knowledge items rated in the top 20 included nine related to evaluation (ranked 1, 2, 6, 7, 9, 10, 11, 13, and 15), three items related to treatment (ranked 3, 8, and 14), one related to the personality of the psychiatrist (ranked 4), four related to specific syndromes such as geriatrics, children, or emergencies

TABLE 2. Agreement Between 223 Psychiatric Practitioners and 257 Psychiatric Department Chairmen and Training Directors on Knowledge Necessary in a Psychiatrist

Knowledge	1987 Agreement (%)	1987 Rank	1980 Rank
Characteristics of and explanations for psychotic, neurotic, characterological, and borderline disorders	94.2	1	3
Criteria for differentiating between organic and functional disorders	94.2	2	1
Indications, contraindications, presumed mechanisms, dosing schedules, and side effects for common psychopharmacological agents	93.9	3	2
Principles of medical ethics related to psychiatry (2)	93.9	4	
Evaluation and management of psychiatric emergencies	93.7	5	5
Differential diagnosis of psychiatric syndromes	93.5	6	4
Descriptive psychiatry, including various clinical syndromes	93.3	7	7
Indications and contraindications for hospitalization	93.3	8	6
Nosology and classification of mental disorders, including childhood disorders	93.3	9	14
Major biochemical theories of psychopathology	92.9	10	15
Psychiatrically pertinent aspects of neurology	92.7	11	16
Psychological aspects of stress, coping, and adaptation, including dying, bereavement, and other life crises	92.5	12	17
Specific syndromes of importance in consultation psychiatry	92.1	13	11
Indications and contraindications for various types of psychotherapy (individual, family, marital, social)	91.7	14	10
Indications and limitations of psychological assessment	91.7	15	35
Genetic and dynamic formulations, including precipitating stress, interpersonal relationships, character structure, psychodynamics, and effects of illness on others	91.4	16	8
Principles of evaluation and intervention in geriatric psychiatry[a]	91.4	17	
Principles of human growth and development, including major theories and biopsychosocial considerations	91.4	18	9
Common psychiatric problems of childhood[a]	91.2	19	26
Principles of the evaluation of children and their families[a]	90.0	20	30
Basic psychoanalytic concepts and theories[a]	89.8	21	24
Psychosomatic theories on pathogenesis and evaluation and therapies of psychosomatic disorders	89.6	22	20
Basic concepts of family organization and communication	89.2	23	28
Forensic psychiatry, including patients' rights, commitment, privileged communication, testamentary capacity, and competency[a]	88.9	24	27
Indications, contraindications, and theories regarding mechanism of action of ECT	88.9	25	
Theories of therapy, indications and contraindications, basic assumptions, and data about outcome	88.5	26	
Psychotherapies: psychoanalytically oriented psychotherapy	88.1	27	12
Basic concepts of psychiatric epidemiology	87.7	28	36
Adolescence with a focus on personality developmental theories[a]	87.5	29	23
Basic concepts of group dynamics	87.5	30	34
Major theories of addiction	87.5	31	
Psychotherapies: group therapy	87.1	32	13
Principles of intervention in child and adolescent psychiatry[a]	86.9	33	31
Psychotherapies: family therapy	86.2	34	19
Evaluation of the merits and limitations of scientific literature	85.6	35	33
Neurobiological basic sciences	85.6	36	32
Models of consultation-liaison psychiatry[a]	85.0	37	18
Physiology of sleep and sleep disturbances	85.0	38	40
Psychotherapies: couples therapy	83.9	39	21
Basic concepts of social psychiatry	81.4	40	36
Basic principles of learning theories	80.6	41	37
Psychotherapies: cognitive therapies	79.8	42	
Psychotherapies: behavior modification	77.7	43	25
History of psychiatry	76.9	44	39
Principles of preventive psychiatry at the community and clinical levels	76.9	45	
Community mental health, including consultation and program evaluation	74.4	46	38
Psychiatric problems of specific ethnic and underprivileged groups	74.3	47	
Mental retardation, including evaluation and treatment planning[a]	70.6	48	41
Psychotherapies: child therapy[a]	67.5	49	22
Psychiatric economics: patterns of private and public funding, reimbursement	65.2	50	
Principles of psychiatric administration[a]	61.9	51	

[a]More than 50% of each group considered this an important aspect of a psychiatric subspecialty.

(ranked 5, 17, 19, and 20), and three related to an area that might be called basic psychology (ranked 12, 16, and 18).

The items that were ranked more important in 1987 than in 1980 included indications for psychological assessment, which moved from rank 35 to 15; knowledge about common psychiatric problems of children, which moved from 26 to 19; and knowledge of the principles of the evaluation of children, which moved from 30 to 20.

The knowledge items that were reduced in order of importance in the rankings included genetic and dynamic formulations, which moved from 8 to 16; growth and development, which moved from 9 to 18; psychoanalytically oriented psychotherapy, which moved from 12 to 27; group psychotherapy, which moved from 13 to 32; family therapy, which moved from 19 to 34; models of consultation-liaison psychiatry, which moved from 18 to 37; couples therapy, which moved from 21 to 39; behavior modification, which moved from 25 to 43; and child therapy, which moved from 22 to 49. Many of the psychotherapy groupings were notably reduced in the ranking of their importance.

Subspecialization

More than 50% of the 223 practitioners listed four skill items and 11 knowledge items that should be considered part of a subspecialty in psychiatry. More than 50% of the 200 training directors listed nine skill items and eight knowledge items as important aspects of a psychiatric subspecialty. More than 50% of the 57 department chairmen considered seven skill items and seven knowledge items important aspects of a psychiatric subspecialty. Items considered essential to a subspecialty by more than 50% of each of these three groups are indicated in tables 1 and 2.

The content of the skill and knowledge items determines the major subspecialties as child psychiatry, adolescent psychiatry, psychoanalysis, geriatric psychiatry, forensic psychiatry, consultation-liaison psychiatry, treatment of alcohol and/or drug dependence, and administrative psychiatry.

DISCUSSION

Since the 1980 report in which psychiatric teachers and practitioners defined the psychiatrist as a generalist skilled in evaluation and treatment of mental disorders, there have been remarkable advances in the field. Discoveries in neural sciences and more effective psychopharmacological techniques have moved psychiatry from a predominantly psychosocial orientation to one that is more biological. Although this is often described as "remedicalization," we prefer to think that the medical identity was never abandoned and that the psychiatric model is more balanced now and includes the "bio" in biopsychosocial. This remedicalization is largely a consequence of the shift of practice from the psychiatric hospital to the general hospital and the resulting increased association with other medical specialists, which reinforces the psychiatrists' medical identity. The enhanced use of the consultation-liaison model has also contributed to this change.

Economic policies have affected all of health care: more attention has been devoted to cost than quality. Limits in coverage of psychiatric illness have created a shift toward brief therapy and a crisis-oriented approach. Long-term therapy and treatment aimed at overcoming problems that diminish the quality of life have given way to treatment for serious psychotic disorders that inhibit normal functioning or produce dramatic symptoms such as severe depression, hallucinations, or delusions. Threats to life and functioning are deemed the only reasons for treatment. The consequence has been the redefinition of needed skills as found in this survey. Skill in long-term therapy aimed at insight has been shifted to the subspecialty of the psychoanalyst.

Another probable explanation for the changing definition of a psychiatrist is the shift in the use of psychiatric time. It has been estimated that 70% of psychiatric time used to be devoted to office psychotherapy for personality disorders and neurotic inhibitions. The shift in caseload to the more seriously ill has been a consequence of cost containment and changed third-party coverage of psychiatric services, the shift from treatment in psychiatric hospitals to general hospitals, and increased knowledge about the psychotic disorders and their treatment.

A diminution in the popularity of the social therapies is also reflected in the responses of those surveyed. In part this has been due to lack of coverage by third-party payers, lack of scientific proof of efficacy, and the consequence of other mental health professionals claiming these therapies as their own special domain.

Another reason for changes in the definition of a psychiatrist is related to the altered popularity of the community mental health movement. The focus on prevention has diminished because of the lack of evidence for its efficacy and because of the withdrawal of support for preventive services. One consequence is a shift to higher priorities for skills and knowledge in direct services and to lowered priorities for community consultation and social therapies associated with community mental health.

Increased attention to humanistic and compassionate attributes and ethical behavior has been characteristic of many physician groups. Specialty boards such as the American Board of Internal Medicine have developed rating systems for humanistic and ethical behavior. APA has given these matters considerable attention in organizational and scientific meetings. Charges of unethical behavior have received considerable publicity. Government, both as payer and licenser, has publicized and punished transgressors. A recent law calls for a federal registry for information on physicians who have been convicted of unethical behavior. The increase in malpractice suits and the cost of malpractice insurance further emphasizes ethical standards. This is reflected in the high ratings given to items reflecting the psychiatrist's personality characteristics.

Subspecialization

The replication of the 1980 ratings points to the increase in subspecialization in psychiatry and the other medical specialties. We do not consider these ratings a sensitive measure of the specific content (knowledge or skill) in each field but only a gross estimate of the importance of subspecialties in psychiatry. Our conclusion is that the subspecialty fields of child psychiatry, adolescent psychiatry, psychoanalysis, geriatric psychiatry, forensic psychiatry, consultation-liaison psychiatry, treatment of alcohol and/or drug dependence, and administrative psychiatry were acknowledged by large numbers of teachers and practitioners (3). Further study of the required knowledge and skills in the subspecialties would require a different approach and should be accomplished with subjects who are skilled in the specific subspecialties. For the present, it is enough to demonstrate that subspecialization is important.

Assessment of Skill and Knowledge of a Psychiatrist

How do those charged with the responsibilities of educating and certifying the competence of psychiatrists determine whether the required skills and knowledge have been acquired and whether they are used in practice (4)? The assessment of competence and the potential for performance used to be done primarily in a cross-sectional fashion during the residency and at the time of Board certification examinations and was accomplished by subjective ratings with a variable amount of rater training. This system has been criticized for failing to assure validity and reliability. The changing nature of the practice of psychiatry today calls for more frequent and ongoing assessments, including assessments of actual performance in practice. Hospital medical staffs review privileges at least biennially. Fifteen of the 23 medical specialty boards have instituted time-limited certification. Several states are considering plans for including competence assessment in reregistration of licenses. We therefore describe current approaches to assessment of clinical competence that might be used to examine the list of skills and knowledge items defined as requirements by this national survey.

Generally, assessment of knowledge—cognitive assessment—is easier than measurement of skill. Techniques of cognitive testing are well developed and well accepted. In psychiatry, standardized tests of knowledge include the Psychiatric Resident In-Training Examination (PRITE), the Psychiatric Knowledge and Skills Assessment Program (PKSAP), and Part I of the American Board of Psychiatry and Neurology examinations. Such cognitive tests are relatively easy to construct and score. They are more useful and reliable if used nationally. For each residency program or hospital to construct its own would be wasteful and would lack the advantage of national norms.

Measures of the personal characteristics of the psychiatrist are best accomplished by ratings provided by those familiar with the work of the person being rated. Such ratings should reflect behavior over a period of time. Raters should be trained carefully; multiple ratings increase the likelihood of reliable data (5).

With respect to the assessment of clinical skills, several options are available, but only some of these have been systematically used in psychiatry. A log of clinical experiences (manual or computerized) during residency is important, if only to document that the trainee has had experience with essential clinical procedures. Such a log should be a record of patients who have been evaluated and treated and should include data on diagnosis, demographics, and treatment as well as outcome. It is also useful for the practitioner to keep such records. A number of medical specialty boards already use such data as part of their certification and recertification processes.

Assessment of clinical skills has become more standardized as a result of technological and procedural advances. One of the most promising technologies is the interactive videodisc-microcomputer combination, which permits an examinee to replicate the clinical process in an uncued fashion. Standardization and high security have made it possible for such tests to be given at many locations at a time convenient for the examinee. Examples include the computer-based examination (CBX) of the National Board of Medical Examiners (6), the DxTER method of Intelligent Images (personal communication from D.M. Allen of Intelligent Images, San Diego, 1986), and the National Library of Medicine method developed by Harless. Such systems can simulate various kinds of patients, interviews, and a variety of approaches to patient-psychiatrist interaction. With videodisc it is possible to film simulated patients, thereby making the tests very realistic experiences. Thus, evaluation and treatment skills for a variety of patients can be tested with this method.

Individuals can be trained to simulate patients in evaluation exercises. The groups that have had the most experience in this area are Stillman et al. (7) and Barrows (8). Although actors simulating physical diseases have been used more often than those simulating psychiatric disorders, these techniques can work as well for our specialty. A simulated patient permits precise examination of the interactions between the psychiatrist and the "patient."

Chart-stimulated recall is a technique in which trained examiners assess the treatment of the psychiatrist's actual patients against accepted standards using the charts of patients treated by the examinee. This technique, which has been used most notably by Maatsch et al. (9) in the field of emergency medicine, has promise for other clinical disciplines.

Ratings by peers, other health professionals, and patients have proven useful in the evaluation of the clinical skills of internists. Using these techniques, Ramsey has shown significant differences between certified and noncertified specialists (1987 personal communication, Department of Internal Medicine, University of Washington School of Medicine). Such ratings can certainly be adapted to psychiatry to measure a variety of clinical skills.

The Objective Structured Clinical Examination is an examination used to measure specific aspects of clinical skills in about 20 short (5–15 minute) sessions dealing with a skill or knowledge item (10). It has been used for medical students and residents in several specialties and can be developed for practitioners. Evaluation and treatment skills for a variety of conditions can be measured in this fashion, which has the advantage of increased reliability by virtue of the number of cases or stations.

Outcome studies are the ultimate evaluation technique. The Joint Commission on Accreditation of Hospitals is committed to development of institutional assessment, and the American Board of Medical Specialties is interested in individual physician performance assessment. Outcome assessment can be done by using hospital data and office chart data and by measuring adjustment, symptom change, and patient satisfaction (among other variables) for a carefully defined sample of patients. Although not easy or inexpensive, this method of skill assessment is the ultimate goal of many who are concerned with performance evaluation (11).

The single Part II examination of the American Board of Psychiatry and Neurology uses cross-sectional techniques that include live patient and audiovisual examinations under direct observation. Although the reliability of the examination ought to be further increased by standardization of the patients and more training for examiners, it continues to be a useful measure of clinical skill. It is now common for residency programs to give mock oral examinations during training. Such practice sessions have the advantages of training and desensitization and are a useful educational device; they provide early feedback to residents and programs about potential difficulties and permit opportunities for remedial work if necessary during training.

With the delineation of knowledge and skill competencies for psychiatry in hand, the profession should now determine which of these many methods of assessment can most effectively and efficiently help us assure that trainees and practitioners are competent and help them achieve even higher standards of practice.

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Training in Geriatric Psychiatry: Will the Supply Meet the Demand?

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The number of geriatric patients with major psychiatric disorders is expected to grow along with the rising proportion of people age 65 and older. Despite recognition of this growth and increases in the training of geropsychiatrists, the supply of specialists is unlikely to keep up with the demand. The authors argue for greater resource expenditure in fellowship programs and a focus on training academic leaders to serve as role models for general psychiatrists and other primary care givers.

(Am J Psychiatry 1988; 145:476–478)

Thanks in part to advances in modern medicine and socioeconomic changes of the twentieth century, we find ourselves living in a "graying" society. The 1980 U.S. Census counted 25 million people in the 65 years and older age group, which represented 11% of the population. The estimate for 1985 was 29 million. Census Bureau projections predict a rise in this number to 35 million by the year 2000 and to at least 64 million by 2030 (1). Unfortunately, as our older population increases, so will the number of elderly people suffering from major mental illness. Because of limitations in epidemiologic data, the prevalence of major psychiatric illness among the elderly is not known (2). Conservative estimates, however, suggest that at least 4% of the people 65 years of age and older have an organic mental disorder, while an additional 15% suffer from such psychiatric illnesses as depressive and anxiety disorders (2–6). Unless a major scientific breakthrough offers a cure for these prevalent disorders, we can expect these illness rates to hold for the year 2030, when the group of mentally ill elderly persons, by conservative estimates, will approach 13 million.

Who will care for this growing number of mentally ill? Who cares for the 5 million or so elderly mentally ill now? Today and, most likely, tomorrow, it is primarily the generalist—the internist, general practitioner, family physician, general psychiatrist, neurologist—who looks after only a fraction of those needing care. Although some primary care physicians have developed some geriatric/gerontological expertise through the "learning-by-doing" method, the growth of specialty training programs in geriatric psychiatry has not kept pace with the need for specialists. We are alarmed about trends for the future.

According to a report by the University of California, Los Angeles, and the Rand Corporation, in 1977 the average psychiatrist spent only 5.3% of total patient care time devoted to people 65 years and older (7). The report noted that in that year alone, there was a need for 1,130 geropsychiatrists (7). Others have estimated an even greater need—for 6,155 geropsychiatrists—on the basis of 1981 prevalence rates of mental illness (8). Although currently there are approximately 800 members of the American Association for Geriatric Psychiatry, only a fraction of that number of psychiatrists with experience and interest in treating the elderly have received specialty training in the form of a formal fellowship program (9).

Over the past decade the medical community's awareness of the need for trained geropsychiatrists has led to a steady growth in the number of training programs. In 1980 the 13 existing programs offered

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both 1- and 2-year fellowships and graduated 12 geropsychiatrists. By 1984 the number of programs had increased to 17, with 34 geropsychiatrists graduating that year. As of 1985 there were 21 training programs with 52 available fellowship positions (9).

The National Institute of Mental Health (NIMH) is charged with training academic leaders in geropsychiatry. Its programs train new geropsychiatrists and geropsychologists and produce faculty for clinical training, research, and postgraduate specialty training. In 1986 these training efforts produced 37 physician specialists; however, funds needed to maintain and expand current programs far exceed available federal support. The NIMH currently has 15 to 17 fundable programs with high priority scores that are awaiting appropriation (10).

To get some idea of future manpower supply, we might assume that the current rate of program expansion continues, i.e., each year's fellowship class has five graduates more than the previous year's class. If so, we can expect approximately 6,000 geropsychiatrists by the year 2030. Yet, even with continued expansion at the current rate, we would only begin to meet projected needs. If we assume that each of these 6,000 geropsychiatrists treated *only* the predicted 13 million mentally ill elderly and practiced 50 hours per week and 50 weeks per year (a total of 2,500 hours per year), these busy practitioners would have a total of 70 minutes for an entire year to evaluate and treat each patient. A more realistic assumption would be that the number of training programs remains at the current level (i.e., 34 graduates per year). If so, just over 1,900 geropsychiatrists will have been trained by the year 2030. Rather than 70 minutes, the average, fully trained geropsychiatrist will have only 20 minutes each year to spend with a patient. Unless technological advances of the twenty-first century drastically curtail the amount of time needed to adequately care for the complicated problems of this special patient group, the supply will not meet the demand.

These figures are estimates based on several assumptions. A variety of factors will influence patient/geropsychiatrist ratios. For example, the present cohort of the elderly is comprised of people who are reluctant to seek psychiatric treatment. Many believe that only "crazy people" see psychiatrists. Today's middle-aged and young adult populations may have a more positive attitude toward psychiatric intervention when their generations reach the upper age groups; this would result in a relative increase in the demand for care. It is impossible to predict precisely how these attitudes, along with such other factors as health care costs and distribution of resources, will ultimately influence the future needs for geropsychiatric care.

Federal and state support for undergraduate medical education is also diminishing. Federal dollars accounted for only 24.5% of medical school revenues in 1983–1984, nearly half the percentage for 1970–1971 (11). For graduate education, the Consolidated Omnibus Reconciliation Bill of 1986 (PL 99–272), known as COBRA, contributes much-needed assistance. According to this bill, Medicare provides direct medical education funding for residency and fellowship training. A formula counts geriatric medicine fellows as a 1.0 full-time equivalent for 2 years to a maximum of 5 years; those in other internal medicine subspecialty fellowships count as a 0.5 full-time equivalent in their second year of training (10). In psychiatry, the percentage of elderly patients treated in the hospital determines the amount that Medicare will reimburse that hospital for trainee salaries. In some psychiatric hospitals, existing administrative structures have led to Medicare funding for only general psychiatry residents and child psychiatry fellows—ironically, geropsychiatry fellows receive none! Geriatric psychiatry faces an additional obstacle. COBRA specifies that reimbursement of graduate training requires that a program be formally approved. Although general psychiatry programs already have a formal approval mechanism, none exists for geriatric psychiatry fellowships.

A geropsychiatrist for every geropsychiatric patient is not a feasible solution given current and projected resource limitations. Others have suggested the training of a relatively small number of geriatric specialists as role models and teachers (12). The Institute of Medicine Committee on Leadership for Academic Geriatric Medicine concluded that limited resources must be focused on "centers of excellence," so that program development and training can yield the highest-quality trainees. Following the challenge of "training the trainees" would be the distribution of these academic leaders—combined teachers, clinicians, and investigators—throughout the nation's medical schools. Their mission, then, would be to enrich existing geriatric curricula in medical schools as well as in "generalist" residency programs (primary care specialties as well as psychiatry).

Additional support for geropsychiatry fellowships will not completely resolve the discrepancy between supply and demand unless such support is drastically increased. In conjunction with expanded subspecialty training, more focused efforts in residency training and continuing medical education of generalists (both psychiatric and nonpsychiatric) are necessary, including a more fully developed geriatric curriculum in medical schools. Crucial to any solution, however, is recognition and resolution of the relative absence of geropsychiatry faculty in training institutions. Without such faculty, the problem will persist. The supply of generalists and specialists will never meet the demand for the care of this rapidly growing number of elderly patients.

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Perceptions of Parenting in Childhood and Social Support in Adulthood

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A group of primiparous women in Australia rated their parents' attitudes and behaviors toward them as children as well as perceived levels of social support shortly after the birth of their first child and 1 year later. After any bias that might have been introduced by neurotic perception of interpersonal relationships had been controlled for, analyses showed a consistent link over time between reports of perceived deficiencies in both maternal care during childhood and in the availability of close supportive relationships during adulthood. This study supports and extends findings from a 1986 U.S. study.

(Am J Psychiatry 1988; 145:479–482)

The view that early socialization experiences in the family contribute to the quality of adult interpersonal relationships underlies psychoanalytic, object relations, self psychology, and attachment theories, as noted by Flaherty and Richman (1) in a rare empirical study of the proposition. Their sample of 211 medical students completed two self-report measures of current social support and early parenting. One of these measures, the Social Support Network Inventory, consisted of 11 items "concerning the five most important members in the respondent's social network and tapping aspects of availability, instrumental support, emotional support, event-related support, and reciprocity." Perceived parenting was measured by the Parental Bonding Instrument (2), a 25-item questionnaire that generates scores on measures of care and protection for each parent as perceived by the recipient during his or her first 16 years. Despite age-specific and developmental variations in parenting, this instrument assumes that there is some consistency over time in the expression of its broad dimensions and that the scales reflect an aggregate of innumerable experiences (2). (See reference 3 for a discussion of the reliability and validity of this instrument.)

Flaherty and Richman (1) hypothesized that respondents reporting low parental care and parental overprotection on the Parental Bonding Instrument would also report lower scores on current social support and that such links would be stronger in relationship to mothers than to fathers, in view of the traditional greater involvement of mothers with their children. The key results were that low scores for parental care, particularly for maternal care, were linked with lower scores for adult social support, but there was no association between parental protection and adult social support ratings.

While the authors acknowledged the need for a more complex conceptualization of social support, they concluded that results from their study were consistent with the psychodynamic assumption that the perceived level of care in early relationships with parents is linked to the perceived quality of subsequent adult social support systems. Emphasis on the word "perceived" is appropriate because the authors recognized that their positive finding could have been determined by a general response style which influenced judgments of both past and present relationships and which created a noncausal association between scores on the two measures. Since scores on perceived levels of current social support were not linked with scores on the parental protection scale and since the link between parental care and current social support was

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stronger for maternal than for paternal relationships, a general response bias was held to be unlikely.

Before the clinical implications of that preliminary research are considered, it is important, first, to determine if the broad findings can be replicated and, second, to explore further the possibility that findings might be invalid as a consequence of a general response style influencing scores on both the presumed predictor and outcome variables. We therefore report a study addressing those two objectives.

METHOD

We examined the key propositions within a large controlled study of interventions for primiparous women designed to determine whether professional or lay support interventions were effective in lowering anxiety levels in mothers with high levels of trait anxiety. For the current study, we used subjects from both the intervention and control groups of the original study. To investigate the possibility of a general response bias, we decided to measure the subjects' neuroticism because of the demonstrated utility of such a measure in similar research inquiries. Henderson et al. (4) assessed the extent to which social networks, both quantitatively and qualitatively, might expose an individual to neurotic decompensation. Although they found links between lack of social support and neurosis, such links largely disappeared when they controlled for Eysenck Personality Inventory (5) neuroticism scores. These researchers observed that neuroticism dominated equations linking background and personality factors to illness. In essence, they suggested that quantitative decrements in social support systems are far less important than perceived qualitative deficiencies in contributing to neurosis, while vulnerability to neurotic decompensation is far more likely to be determined by personality variables (especially neuroticism) than by actual anomalies in the social network.

On the basis of these findings, we chose the Eysenck Personality Inventory neuroticism measure for use in our study. We have already reported that although our group of highly anxious mothers was more likely to report high levels of recent life events and less social support as well as negative interpretations of their pregnancy, the hospital experience, and the hospital staff, such variables were less discriminating when neuroticism levels in the mothers were effectively controlled.

In assessing interpersonal relationships, we used the same measure of parenting (the Parental Bonding Instrument) used by the U.S. researchers but chose a different measure of social support (1). We used the Interview Schedule for Social Interaction, developed by Henderson et al. (4) in Australia. There are corroborative reports (4) offering some support for the validity of this instrument. In essence, scores are determined after a semistructured interview that assesses close attachment figures, friends, acquaintances, and work associates, so that the respondent's primary group is assessed in terms of both the availability of social relationships and their perceived adequacy. Four principal subscale scores are determined. The availability of attachment subscale assesses the availability of intimates and close supportive friendships on which the respondent believes that he or she may lean or in whom he or she may confide. The adequacy of attachment subscale assesses the perceived adequacy of that set of relationships. The availability of social integration subscale assesses the availability of more general relationships that occupy less intimate positions in the social network, and the adequacy of social integration subscale assesses the perceived adequacy of this social network component.

In summary, the study group (6, 7) included a consecutive series of primiparous women who were asked to complete trait and state anxiety scales on the third or fourth day after giving birth; exclusion criteria were specified. Six hundred thirty women were approached to obtain subgroups stratified by varying levels of trait anxiety. Of the 166 subjects so selected, 152 were interviewed; complete information was available for all but five of these women over the 12-month study.

Subjects were interviewed in their homes within 3 weeks of discharge from the hospital and asked to rate both their perceptions of parental care and protection that they had received as children on the Parental Bonding Instrument and their perceptions of current social support on the Interview Schedule for Social Interaction. They also completed the Eysenck Personality Inventory neuroticism scale. Twelve months later the subjects again completed the Interview Schedule for Social Interaction and the Eysenck Personality Inventory neuroticism measures. The data were collected at a time of stress—in the first few weeks after the birth of a child—and 1 year later to examine links between perceptions of parenting in childhood and social support levels in adulthood.

RESULTS

Our final study group was composed of 129 women. Most of the 18 women not included were excluded because they were unable to complete the paternal Parental Bonding Instrument scale.

Baseline scores for social support on the Interview Schedule for Social Interaction were correlated with both maternal and paternal Parental Bonding Instrument scores for care and protection. If there was a general response bias that determined the way in which subjects perceived important interpersonal relationships, it might be expected that significant associations would be generated for all examinations. However, on three of the Parental Bonding Instrument scales (maternal protection, paternal care, and paternal protection), the correlation coefficients (df=127) were extremely low (ranging from 0.01 to 0.13), suggesting the absence of any general interpersonal response bias. Parental Bonding Instrument maternal care scores were significantly linked, however, with availability of attachment scores ($r=0.27$, $df=127$, $p<0.001$) and with availability of social integration scores ($r=0.16$, $df=127$, $p<0.05$). After partialling out Eysenck Personality Inventory neuroticism scores from all intercorrelations, only one significant association remained: maternal care scores remained positively correlated with availability of attachment scores ($r=0.25$, $df=127$, $p<0.001$).

Twelve-month Interview Schedule for Social Interaction scores were also intercorrelated with Parental Bonding Instrument scale scores. At 12 months there were weak negative associations linking higher maternal protection scores with lower availability of attachment ($r=-0.15$, $df=127$, $p<0.05$) and availability of social integration scores ($r=-0.16$, $df=127$, $p<0.05$). Additionally, maternal care scores were positively linked with availability of attachment ($r=0.15$, $df=127$, $p<0.05$) and availability of social integration ($r=0.26$, $df=127$, $p<0.001$) scores. Only one of these four significant associations remained after Eysenck Personality Inventory neuroticism scores assessed at the 12-month follow-up were partialled out of the associations: maternal care again was positively linked with availability of attachment scores ($r=0.24$, $df=127$, $p<0.001$).

DISCUSSION

Despite the fact that we used a different social support measure, our findings replicate and refine the general conclusion of Flaherty and Richman (1). Our measure of social support was designed to assess support provided both by intimates and by more distant social support figures and assesses both the quantitative availability and qualitative adequacy of each support level. The U.S. researchers used a measure that generated a single score and was weighted more toward intimates and close affiliates than to the broad social network, with an emphasis on the perceived adequacy of that support. Both studies have shown a link between high scores for the early experience of maternal care received by the subjects and high scores for current levels of social support.

Our findings suggest some specificity to the general proposition. After we controlled for neurotic perception, only one of the four parental scores (maternal care) was linked with only one of the four social support measures (availability of attachment). Although this was not a strong association, it is unlikely that the link was a chance one because we found it to be a consistent association in two sets of tests. Furthermore, it is consistent with findings from the U.S. study. The availability of attachment measure essentially assesses whether the respondent has some certainty about continuation of a single lasting relationship with an intimate whom the respondent can lean on, feel close to, and share happiness and private feelings with and who is able to comfort the respondent (4). The general conclusion of both these studies is that the experience of receiving adequate maternal care in childhood disposes the child to perceiving subsequent intimate relationships as satisfactory in adulthood but not necessarily to perceiving relationships of greater satisfaction in wider social networks.

The suggested specific relevance of mothers is of interest. In an earlier study of patients with neurotic depression (8), the data suggested that subjects were more sensitive to anomalous parenting from their same-sexed parent, a phenomenon which could explain our present findings. The findings also suggest greater involvement by mothers in the early socialization process, as argued by Flaherty and Richman (1) in their mixed-sex sample of respondents, or possibly the existence of a hierarchy of internalized working models in the child of which the mother often stands foremost—as recently considered by Main et al (9).

Although Flaherty and Richman reported a link between early parenting and adult social support levels, they conceded that a patient's response style could have distorted perceptions of both past and current relationships and brought about a noncausal link. For this reason, we examined the effect of partialling out Eysenck Personality Inventory neuroticism scores, noting the views of Henderson et al. (4). In examining the extent to which quantitative and qualitative deficits in social networks might contribute to neurotic decompensation, Henderson et al. (4) included the Eysenck Personality Inventory neuroticism measure in a number of studies and found evidence that this personality measure made a significant contribution to a number of their analyses. In fact, when personality variables were controlled, the quantitative aspects of the social network made only a negligible contribution to the explanation of illness in their study. In an earlier report (6), we established that our subjects with high levels of anxiety could be distinguished from subjects without high levels of anxiety on a number of variables, including the reporting of life events and lower scores on the availability of social integration subscale of the Interview Schedule for Social Interaction measure. However, when we controlled for neuroticism, these two variables were minimized, suggesting that scores on those two measures had been spuriously raised by more "neurotic" subjects. This again supports the utility of the Eysenck Personality Inventory neuroticism measure in assessing negative perceptions of interpersonal relationships and in minimizing confounding effects of neurotic perception in statistical analyses.

Flaherty and Richman (1) suggested that their data were "congruent with the psychodynamic assumption that later affective modes of relating are linked to the quality of earlier object relations." If this hypothesis is supported now by results from two empirical studies, an important issue is the extent to which early object relationships contribute to perceptions of close adult relationships (i.e., contribute to internal representations of intimate figures) and/or to the actual selection of an adult intimate. Rutter (10) has considered mechanisms involved in developmental continuity and discontinuity and reviewed empirical studies which suggest that parenting experiences in childhood influence the choice of spouse, although this influence can be modified. Brown et al. (11) have developed a model incorporating both Bowlby's views (12) and data from their Walthamstow study to explain links between the early parental environment and adult depression, a model that suggests links between early levels of parental care and social support in adulthood. They accept Bowlby's views that three kinds of parental experience in childhood (failure to attain a stable and secure relationship with parents; exposure to parents who suggest that the child is unlovable, inadequate, or incompetent; and parental loss) dispose to a sense of hopelessness and helplessness (12). Brown et al. (11) suggested that a lack of parental care promotes a personality style of "childhood helplessness" and leads to premarital pregnancy and that those two variables dispose to being in a lower social class in adulthood, a vulnerable style of adult "attachment," and a degree of "helplessness"—variables which expose the individual to a high rate of provocative agents and to depression. The extent to which adverse early parenting disposes to anomalies in intimate adult relationships is an important research issue in its own right that, if clarified by specification of the mediating variables, has considerable functional implications.

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Differential Memory Function With Dopaminergic Versus Anticholinergic Treatment of Drug-Induced Extrapyramidal Symptoms

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Nine chronic schizophrenic patients being treated with high-potency antipsychotic medication and antiparkinsonian agents were enrolled in a double-blind, crossover trial comparing amantadine and trihexyphenidyl. Memory function was assessed with the Rey Auditory-Verbal Learning Test during each 6-week drug trial. The subjects performed significantly better while receiving amantadine. Examinations of computed tomographic studies of seven subjects revealed a significant inverse correlation between ventricle size and memory while they were taking trihexyphenidyl but not amantadine. This suggests that patients with underlying brain pathology may be particularly vulnerable to the memory-disrupting effects of anticholinergic agents.

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The treatment for neuroleptic-induced extrapyramidal symptoms traditionally includes the use of synthetic anticholinergic agents (1). Although effective in treating extrapyramidal symptoms, the synthetic anticholinergic antiparkinsonian drugs do have adverse effects of their own. They frequently produce atropine-like side effects that may add to the anticholinergic side effects of the neuroleptics (2). Anticholinergic activity is associated with a host of autonomic symptoms during both administration and withdrawal (3). In addition, anticholinergic agents have been shown to impair short-term memory processes in both animals and man (4). The degree of serum anticholinergic activity in patients on neuroleptic regimens (including anticholinergic treatment of extrapyramidal symptoms) has been directly correlated with impairment of short-term memory on a test of short-term memory (5). Discontinuation of anticholinergic treatment for extrapyramidal symptoms has been associated with improved performance on the Wechsler Memory Scale, according to Baker et al. (6).

Amantadine hydrochloride is an antiviral drug believed to have dopaminergic action. It is effective in the treatment of Parkinson's syndrome (7) and has been shown in uncontrolled (8) and controlled (9–11) studies to be as effective as anticholinergic agents in the alleviation of neuroleptic-induced extrapyramidal symptoms. It has recently been demonstrated (12) that amantadine causes less impairment in the memory function of elderly normal subjects than trihexyphenidyl. However, we know of no such study involving patients being treated clinically for drug-induced parkinsonism. Such a differentiation might have clinical significance, particularly if it could help minimize dysfunction in a population whose cognitive function already is seriously compromised. We therefore undertook a double-blind, 6-week crossover comparison of amantadine and trihexyphenidyl in patients receiving chronic neuroleptic treatment who required antiparkinsonian medication.

METHOD

The study involved nine (eight male) schizophrenic or schizoaffective inpatients (diagnosed according to *DSM-III* criteria) chronically hospitalized in a state mental health facility. Their mean age was 30 years (range=21–46). The subjects were all receiving high-potency antipsychotic medications (mean chlorpromazine equivalents=950 mg/day, range=250–2250 mg/day) and had required antiparkinsonian medication daily for 4 weeks before inclusion in the study. They were maintained on the same doses of antipsychotic medication throughout the study. None had significant medical illness, was pregnant, or required medication with anticholinergic properties to treat disorders other

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than extrapyramidal symptoms (e.g., imipramine for depression). The subjects received the following laboratory tests before admission to the study and then under each drug condition: urinalysis and measurement of blood levels of electrolytes, creatinine, urea, alkaline phosphatase, LDH, SGOT, bilirubin, and glucose. The patients gave signed and witnessed informed consent before entering this study.

Amantadine and trihexyphenidyl were administered in a double-blind, crossover fashion. The drugs were supplied in identical-appearing liquid form; the concentration for amantadine was 100 mg/10 cc, and for trihexyphenidyl it was 4 mg/10 cc. Dose equivalency was established as follows: 2 mg of benztropine=4 mg of trihexyphenidyl=100 mg of amantadine. The subjects were randomly assigned to either amantadine or trihexyphenidyl at doses equivalent to the doses of antiparkinsonian medication they had been receiving before the study. Five began with amantadine, four with trihexyphenidyl. Each phase lasted 6 weeks. The doses were adjusted during the first 3 weeks of the 6-week trial periods to control extrapyramidal symptoms and to minimize side effects but did not exceed 40 cc/day (400 mg of amantadine or 16 mg of trihexyphenidyl). No changes in dose were made in the last 3 weeks of each trial. During this period the mean ± SD dose of amantadine was 233 ± 125 mg/day, and the trihexyphenidyl dose was 8.9 ± 4.1 mg/day.

The patients were seen weekly, at which time they were administered a modified Simpson-Angus Scale (13) to assess extrapyramidal symptoms and a side effects questionnaire (10). In addition, current psychopathology was assessed by two trained raters using the Brief Psychiatric Rating Scale (BPRS) (14) in weeks 4 and 6 of each drug trial. Interrater reliability for the first 20 BPRS observations was adequate ($r=0.76$, $df=20$, $p<0.01$). Because of the suggestion that dopaminergic drugs might reduce negative symptoms (15), the Schedule for Emotional Blunting (16) was completed at the same time as the BPRS.

Memory was assessed with a modified version of the Rey Auditory-Verbal Learning Test (17), which assesses several aspects of memory and learning. The test was modified because of the great distractibility of schizophrenic patients. On the basis of pilot studies performed on other patients in the institution, the word list was decreased to 10 and the list repetitions were decreased to four. The resulting instrument consisted of 1) four learning trials in which the subject was read the list and asked to repeat it after each reading ("acquisition" in the terminology of Drachman and Leavitt [18]), 2) an interference trial consisting of one reading of a different 10-word list and repetition of the list by the subject, 3) a free recall of the initially learned list ("storage"), and 4) a recognition trial in which the subject had to select each initially learned word from among five words including semantically and phonetically related words ("retrieval"). Seven scores were obtained: four learning trials, the interference trial, the free recall trial, and the recognition trial. In total, the test took about 15 minutes to administer. The Rey Auditory-Verbal Learning Test assesses acquisition (incremental changes in response over presentations one through four), memory consolidation into long-term storage (recall trial after the interference list), and retrieval from stored memory (recognition trial).

The subjects received the memory test at the end of the 4th and 6th weeks of each drug trial. Thus, each subject was administered the test at four sessions. To minimize practice effects, two different versions of the test were administered and order of administration was counterbalanced within the groups to control for order effects.

CAT brain scans were obtained with a Siemens Somatom II scanner for seven of the nine patients. Lateral ventricle size was assessed blindly by determining the ventricle-brain ratio (VBR) (19) and comparing it to the mean VBR of headache patients scanned with the same machine and previously described (20).

The data were analyzed to establish differences in mnemonic acquisition, storage, and retrieval. A mixed model analysis of variance (ANOVA) was performed with drug, drug order, session, and trial as factors (21) for the first four acquisition trials. Similar, separate analyses without the trial factor were carried out for the interference, free recall, and recognition trials. An analysis of "forgetting," examining the possible difference between the free recall trial and the last acquisition trial, was carried out with all four factors. The Drug by Trial interaction was examined to determine whether there was a difference in forgetting between the two drugs.

RESULTS

For the first four trials there was a significant trial effect ($F=9.6$, $df=3, 21$, $p<0.001$), indicating acquisition. There was also a significant effect of drug ($F=5.8$, $df=1, 7$, $p<0.05$), indicating an advantage for amantadine. There was no drug order or session effect and no significant interaction. There were also trends favoring amantadine for the interference ($F=4.7$, $df=1, 7$, $p=0.067$) and recognition ($F=4.8$, $df=1, 7$, $p=0.065$) trials. There was no significant drug effect for the free recall trial ($F=0.86$, $df=1, 7$, $p>0.3$) and no significant Drug by Trial interaction for the last acquisition and free recall trials ($F=3.5$, $df=1, 7$, $p>0.1$) to support a difference in forgetting between drugs (see table 1).

We examined the relationship between the CAT findings and performance on the Rey Auditory-Verbal Learning Test. For the seven patients studied, the mean ± SD VBR was 7.0 ± 4.8, and four of the seven had VBRs at least two standard deviations higher than the mean for the age-matched headache control subjects. There was a significant inverse relationship of VBR to mean performance on the learning test (combined acquisition, storage, and retrieval trials) in the trihexyphenidyl condition ($\text{rho}=-0.81$, $Z=1.99$, $p<$

TABLE 1. Scores on the Rey Auditory-Verbal Learning Test of Nine Schizophrenic Patients in Crossover Study of Trihexyphenidyl and Amantadine[a]

	Score on Learning Test			
	Trihexyphenidyl		Amantadine	
Trial	Mean	SD	Mean	SD
Learning				
Trial 1	3.4	1.4	4.6	1.3
Trial 2	4.4	2.0	5.6	1.0
Trial 3	3.9	2.0	6.3	1.7
Trial 4	5.4	2.4	6.4	1.0
Interference	1.5	1.3	2.7	2.3
Free recall	4.3	2.0	5.0	1.6
Recognition	8.0	1.9	9.0	1.1

[a] Significant trial effect ($F=9.6$, $df=3, 21$, $p<0.001$) and drug effect ($F=5.8$, $df=1, 7$, $p<0.05$) for the four learning trials; significant drug effects for the interference ($F=4.7$, $df=1, 7$, $p=0.067$) and recognition ($F=4.8$, $df=1, 7$, $p=0.065$) trials.

0.05) but not the amantadine condition (rho=-0.38, $Z=0.94$) (see figure 1).

There were few significant differences in the measurements of psychopathology between the two drug periods. The mean total BPRS score during the trihexyphenidyl period (16.4 ± 7.8) did not differ significantly from that during the amantadine period (18.6 ± 7.5) (paired $t=0.51$, $df=8$, n.s.). As for specific item clusters, there was no significant difference between trihexyphenidyl and amantadine in psychosis (conceptual disorganization, hallucinations, unusual thoughts) (3.4 ± 3.6 versus 4.5 ± 3.8; paired $t=0.85$, $df=8$, n.s.) or in aggressivity (hostility, suspiciousness) (2.9 ± 1.3 versus 2.8 ± 1.9; paired $t=0.01$, $df=8$, n.s.). There was a trend, however, for the BPRS emotional blunting score to be higher with amantadine (3.0 ± 0.8) than with trihexyphenidyl (2.3 ± 1.3) (paired $t=1.97$, $df=8$, $p=0.07$). This impression was supported by the Schedule for Emotional Blunting, which also showed more symptoms with amantadine (11.9 ± 3.2) than with trihexyphenidyl (9.8 ± 2.9) (paired $t=4.0$, $df=8$, $p<0.01$).

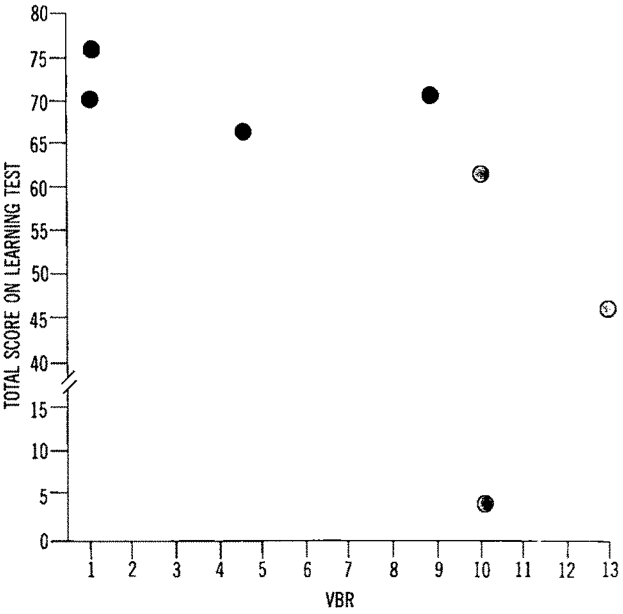
There were no significant differences in side effect measures between the two drug periods. The mean Simpson-Angus extrapyramidal symptom scores did not differ between trihexyphenidyl (4.4 ± 3.1) and amantadine (4.9 ± 3.9) (paired $t=0.01$, $df=8$, n.s.), nor did the mean scores on the side effect scale (21.9 ± 12.1 and 21.9 ± 14.3; paired $t=0.0$, $df=8$, n.s.).

None of the laboratory measures revealed a clinically significant change from baseline on either drug regimen.

DISCUSSION

The primary purpose of this study was to determine whether there was a difference in the effects on memory function of dopaminergic and anticholinergic agents used in the treatment of drug-induced parkinsonism. Our findings suggest better memory function, as assessed by the Rey Auditory-Verbal Learning Test, with amantadine than with trihexyphenidyl treatment. The difference between drug conditions was most apparent in the four acquisition trials, although similar but not significant differences were present in the postinterference and retrieval trials. The difference between the two drug conditions was not significant for the free recall (storage) trial or for a measure of forgetting. The differences between the two drug conditions were similar to but possibly less robust than those demonstrated by McEvoy et al. (12), whose patients were older than ours (mean age of 66 years versus 30 years).

FIGURE 1. Relationship of VBR and Performance on the Rey Auditory-Verbal Learning Test for Seven Schizophrenic Patients Receiving Trihexyphenidyl[a]



[a] Rho=-0.81, $Z=1.99$, $p<0.05$.

The majority of our patients had evidence of significant ventricular enlargement. This is consistent with our previous experience using CAT techniques with chronically hospitalized patients (22). We noted a significant correlation between ventricle size and learning test performance during trihexyphenidyl but not amantadine treatment; as expected, the patients with larger ventricles had poorer performances. Thus, it appears that trihexyphenidyl may interact with a structural abnormality to produce poorer performance.

This finding is consistent with our previous reports that drug-induced side effects, including extrapyramidal symptoms, are more frequent in patients with enlarged ventricles (23). This relationship also suggests that our overall finding of a memory function difference between the two drug regimens might have been detected in this population because of the high frequency of CAT abnormalities. A more neuropsychologically intact patient study group might have shown no significant differences between drug conditions.

Although the effects on memory were in the expected direction, the effects on psychopathology were not. Several lines of evidence, both theoretical (24) and clinical (15), have suggested that dopaminergic agents might ameliorate negative symptoms of schizophrenia. However, we found a trend toward higher scores on the BPRS blunted affect item and significantly higher scores on the Schedule for Emotional Blunting during amantadine treatment. Although it is possible that these findings might reflect poorer control of extrapyramidal symptoms by amantadine, this is not supported by other findings. The total Simpson-Angus scores did not differ significantly between the two drugs, and more important, the ratings on the akinesia item were almost identical in the two drug conditions (amantadine, 0.87±0.86; trihexyphenidyl, 0.93±1.21). An alternative explanation is that the amantadine did not increase emotional blunting but that the trihexyphenidyl, because of its interference with cognition, produced a more aroused or euphoric state. Such an effect of anticholinergic agents has been described in other populations (25). The design of the study does not allow us to be sure which of the two drugs produced the behavioral difference.

Other comparisons of the two drug conditions tended to reveal no significant differences. In particular, we could find no evidence that the dopaminergic agents exacerbated psychoses or increased aggressivity. Thus, our findings in this regard are similar to those noted in previous trials of amantadine for drug-induced extrapyramidal symptoms (9–11).

In summary, we demonstrated that chronic schizophrenic patients perform better on a test of verbal memory during treatment of drug-induced extrapyramidal symptoms with a dopaminergic agent than with an anticholinergic agent. Our data suggest that chronic schizophrenic patients with enlarged ventricles may be particularly susceptible to the cognitive dysfunction associated with anticholinergic agents. Although further work is needed to confirm these findings, in patients with cognitive deficits, especially those with enlarged ventricles, a dopaminergic agent, such as amantadine, might provide certain advantages in the treatment of drug-induced extrapyramidal symptoms.

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Affective and Psychotic Symptoms Associated With Anabolic Steroid Use

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To assess the frequency of affective and psychotic symptoms in athletes taking anabolic steroids, the authors performed structured interviews of 41 bodybuilders and football players who had used steroids. According to DSM-III-R, *nine subjects (22%) displayed a full affective syndrome, and five (12%) displayed psychotic symptoms in association with steroid use. These findings suggest that major psychiatric symptoms may be a common adverse effect of these drugs.*

(Am J Psychiatry 1988; 145:487–490)

Anabolic steroids are widely used by athletes seeking gains in muscle size and strength (1, 2). These drugs produce well-documented adverse medical effects, but their psychiatric effects have rarely been examined. Although some studies have noted euphoria or irritability in association with anabolic steroid use (2), only four reports, to our knowledge, have described more serious psychiatric syndromes. The first (3) described a 17-year-old male bodybuilder who developed depression, paranoid ideation, and "audible thoughts" about 6 months after starting a regimen of unknown anabolic steroids obtained illicitly. The second (4) reported a 27-year-old male bodybuilder who developed euphoria, irritability, racing thoughts, and hyperactivity within a few days of starting oral oxandrolone, 6 mg b.i.d. A third report (5) described paranoid symptoms in four of five depressed men within a few days of taking imipramine plus methyltestosterone; in all four patients, the paranoid symptoms resolved promptly when methyltestosterone was stopped.

Finally, we (6) described two patients who required hospitalization at our center for psychotic affective syndromes associated with anabolic steroid use. The first, a 40-year-old salesman, had been prescribed methyltestosterone, 10 mg b.i.d., for idiopathic impotence. Within 2 weeks he noted severe depression, sleep disorder, anorexia, psychomotor retardation, feelings of guilt, delusions of reference, and visual and auditory hallucinations. After 2 months, methyltestosterone was discontinued, and he began to take amitriptyline, 30 mg/day. Within 5 days he became sleepless, hyperactive, and grandiose and continued to have delusions and hallucinations. Physical examination and laboratory test results, including testosterone, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), B_{12}, and folate levels, sleep and awake EEGs, and a CAT scan at admission were all within normal limits. Amitriptyline was stopped, and the manic and psychotic symptoms resolved within 10 days. At follow-up 32 months later, the patient reported no recurrence of any major psychiatric symptoms. His impotence persisted and remained unexplained; he had taken no further steroids.

The second patient, a 22-year-old construction worker, took two courses (totaling 15 weeks) of methandrostenolone, 5 mg t.i.d., for bodybuilding. While taking the drug, he noted increased irritability, confusion, and difficulty sleeping. After discontinuing the drug, he developed depression, trouble sleeping, nightmares, slight weight gain, prominent diurnal variation that was worse in the morning, chronic anxiety, and moderate agoraphobia. These symptoms lasted 4 months. At the end of this period, he took 20 mg of methandrostenolone and for the next 3 days noted prominent affective lability and, for the first time, delusions of reference. After a few weeks' remission, these symptoms spontaneously recurred and worsened. He believed that his mind was influencing the pictures on television, and he promised to show God to a friend. At admission, physical examination and laboratory test results, including testosterone, FSH, and LH levels, were all normal. The symptoms responded to haloperidol, which was successfully discontinued after 10 weeks. At 24-month follow-up, having used no further steroids, the patient remained asymptomatic and was working full time.

The observations described above suggest that marked affective and/or psychotic symptoms may sometimes occur in individuals who are taking anabolic steroids. To further explore this phenomenon, we recruited and interviewed 41 bodybuilders and football players who had used these drugs.

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TABLE 1. Anabolic Steroid Regimens Reported in Representative Medical Studies and by Subjects in Present Study

Study	Drug	Dose	Duration (weeks)
Representative medical studies			
O'Shea and Winkler, 1970 (10)	Oxandrolone	10 mg/day p.o.	6
Golding et al., 1974 (11)	Methandrostenolone	10 mg/day p.o.	9
Crist et al., 1983 (12)	Testosterone cypionate or nadrolone decanoate	100 mg/week i.m.	6
Present study			
Typical light use	Methandrostenolone	15 mg/day p.o.	6
Typical moderate use[a]	Methandrostenolone	20 mg/day p.o.	10
	Testosterone cypionate	200 mg/day i.m.	10
	Nandrolone decanoate	200 mg/day i.m.	10
Typical heavy use[a]	Methandrostenolone	40 mg/day p.o.	16
	Oxandrolone	40 mg/day p.o.	16
	Methenolone enanthate[b]	4 cc/week i.m.	16
	Nandrolone decanoate	600 mg/week i.m.	16
	Boldenone undecylenate[c]	8 cc/week i.m.	16

[a] All drugs taken simultaneously.

[b] Not legally available for human use in the United States; hence potency is unknown.

[c] Boldenone (Equipoise), one of several veterinary preparations used by the study subjects, is a steroid chiefly used for horses; a dose of 8 cc would represent either 200 or 400 mg of boldenone, since the drug is marketed in two strengths.

METHOD

We sent letters to 38 gymnasiums, 26 in eastern Massachusetts and 12 in Los Angeles, offering $25 for a confidential interview with any individual who had used anabolic steroids. The letter did not reveal that the interview was intended primarily to explore psychiatric symptoms. We recruited a total of 41 subjects—22 subjects in Massachusetts and 19 subjects in Los Angeles.

For each subject, we obtained a lifetime history of anabolic steroids use, the dose, and the duration of use. Steroids are typically taken in "cycles" lasting from 4 to 12 weeks, often involving several drugs simultaneously ("stacking"). Most users provided remarkably precise histories of the dates, drugs, and doses for each cycle. We then inquired about body weight and strength (e.g., the maximum weight that the individual could "bench press" or "squat") before and after each cycle, medical problems experienced while taking steroids, lifetime medical history, and current alcohol, tobacco, and other drug use.

Next we administered the axis I portion of the Structured Clinical Interview for *DSM-III-R* (SCID) (7), asking first the SCID questions about the periods of steroid exposure, i.e., when the subjects were actually taking steroids or within 3 months after stopping them (the latter to allow for withdrawal effects from stopping a cycle), and second about the periods of no steroid exposure, i.e., times other than the periods of steroid exposure. The frequency of various psychiatric syndromes during the subjects' steroid exposure periods and during the no steroid exposure periods was then compared. The significance of these comparisons was tested by Fisher's exact test (two-tailed).

Finally, we asked each subject about his or her family history of psychiatric disorder. Using methods identical to those we have used in previous epidemiologic studies (8, 9), we rated the presence of *DSM-III-R* axis I psychiatric disorders in all first-degree relatives.

All results are reported as mean±SD.

RESULTS

The subjects included 39 men and two women. They ranged in age from 17 to 51 years (26.1±7.1 years). Twelve (29.3%) had first used steroids before age 20; some had used the drugs as early as age 14 or 15. Their lifetime use of steroids ranged from 8 to 240 weeks (45.1±51.5 weeks), representing between one and 30 separate cycles per subject.

Simple observation revealed that the muscle gains achieved by these subjects were dramatic, suggesting that the medical literature may have underestimated the potential of these drugs under conditions of actual use by athletes. For example, an 18-year-old man, 72 in. tall, reported that before steroid use he weighed 135 lb. and could perform the squat (a deep knee bend with a barbell supported on the shoulders) for one or two repetitions with 135 lb. Two years later, at the time of the interview, after four cycles of steroids totaling 55 weeks, he weighed 230 lb. (with a low percent of body fat) and reported a squat of 655 lb.

Such gains may be explained by the high doses of steroids used by the subjects. Table 1 compares the steroid doses reported by subjects from our sample whose typical use was classified as light, moderate, or heavy with the doses reported in three typical medical studies of steroids in athletes (10–12). Although dose equivalency is difficult to estimate, particularly for preparations not legally available in the United States or for veterinary preparations such as boldenone (Equipoise), it appears that many of our subjects routinely used doses 10–100 times greater than those reported in the medical studies.

None of the 41 subjects recalled an adverse medical effect of steroids requiring medical consultation. Reported problems included acne (N=18), temporary testicular atrophy (N=5), gynecomastia (N=3), difficulty urinating (N=2), hair loss (N=3), and, in both of the women, deepening voice. Of course, in their retrospective assessments, some subjects may have minimized or forgotten particular medical complications. Most subjects were very concerned with maintaining good health: only four (9.8%) smoked cigarettes and only six (14.6%) drank more than four alcoholic drinks (1½ oz. of liquor, four oz. of wine, or 12 oz. of beer) per week.

Five subjects (12.2%) met *DSM-III-R* criteria for psychotic symptoms during periods of steroid exposure, and no subject had psychotic symptoms during periods of no steroid exposure (p=0.055). Among the five subjects with psychotic symptoms, one had auditory hallucinations of voices lasting 5 weeks, a second developed the paranoid delusion that friends were stealing from him, two developed delusions of reference, and the fifth developed the grandiose delusion that he could pick up a car and tip it over. Four additional subjects reported mild or equivocal psychotic symptoms (defined as "subthreshold" psychotic symptoms on the SCID) during periods of steroid exposure: two developed paranoid jealousy of their girlfriends, one had mild referential thinking, and one developed pronounced grandiose beliefs. All subjects (N=9) reported a remission of these symptoms within a few weeks after stopping steroids, but none reported psychotic symptoms, even at the subthreshold level, at any time during periods of no steroid exposure, a highly significant difference (p=0.002). All users who experienced psychotic symptoms were "stacking" between two and four steroids, including at least one orally active 17-alkylated steroid, such as methandrostenolone or oxandrolone (known to users as "orals") plus at least one parenteral preparation, such as a testosterone ester or nandrolone decanoate (known as "injectables").

Five subjects (12.2%) met *DSM-III-R* criteria for a manic episode during steroid exposure (except for the *DSM-III-R* exclusion criterion regarding an organic etiology for the symptoms). Eight others (19.5%) only narrowly missed a diagnosis of manic episode; i.e., they met all but one of the first three *DSM-III-R* criteria. No subject reported a manic episode, even at the subthreshold level according to the SCID, during periods of no steroid exposure. Both comparisons were statistically significant (N=5 versus N=0, p=0.055; N=13 versus N=0, p<0.0001). Ten subjects (24.4%) were "stacking" when they experienced manic symptoms, but three were taking methandrostenolone or oxandrolone exclusively.

Several examples illustrate the behavior of subjects whom we scored as manic or subthreshold manic. One 23-year-old man bought a $17,000 sports car while taking methandrostenolone. When he stopped the drug, he realized that he could not afford the payments and sold the car; a year later, during another cycle, he impulsively bought a $20,000 sports car. Another subject bought an old car and deliberately drove it into a tree at 40 miles per hour while a friend videotaped him. Another became enraged when the driver in front of him inadvertently left his directional signal flashing; at the next stoplight, he jumped out and smashed the offender's windshield. Many others described pronounced euphoria and grandiosity, believing that nothing in the world could hurt them. No subject described comparable periods of such behavior during periods of no steroid exposure.

Five subjects (12.2%) developed major depression, according to *DSM-III-R*, while withdrawing from steroids. One of them had a history of major depression before steroid use. To minimize such withdrawal effects at the end of their cycles, many subjects had used human chorionic gonadotropin, a hormone readily available illicitly, to restimulate their endogenous testosterone production. Two subjects (4.9%) developed major depression during periods of no steroid use.

When we combined the subjects who displayed a full manic syndrome with those who displayed a full depressive syndrome, we found that significantly more of our 41 subjects developed a full affective syndrome during periods of steroid exposure (N=9 or 22.0%) than during periods of no steroid exposure (N=2 or 4.9%) (p=0.048). The subjects' past psychiatric histories were unremarkable except for substance use: six (14.6%) reported prior alcohol abuse or dependence, and 13 (31.7%) reported other prior substance abuse or dependence, most commonly cannabis (N=7) and cocaine (N=5). No subject reported current substance abuse or dependence (other than steroids). Finally, one subject (a 40-year-old woman) reported a history of panic disorder. Her typical attacks occurred weekly but remitted promptly when she started using oxandrolone, 20 mg/day.

Seven subjects (17.1%) reported at least one first-degree relative with major affective disorder, but these subjects did not show a significantly higher frequency of affective or psychotic symptoms during periods of steroid exposure than the subjects not reporting such a family history.

DISCUSSION

Our findings must be considered descriptive rather than quantitative, since it is unclear whether our observations were representative of the experiences of steroid users as a whole. It is our impression that, despite our considerable efforts at recruitment, only a minority of steroid users were willing to be interviewed. Thus, we suspect that we were getting only a glimpse of a large underground subculture.

However, we were still able to achieve useful comparisons by using as a control value the frequency of psychiatric syndromes in the subjects during periods of no steroid exposure. This is a conservative approach, since the null hypothesis would predict a higher risk of developing a psychiatric disorder during the longer portion of a subject's life in which there was no steroid exposure than during the shorter portion in which there was steroid exposure. Despite this effect, affective and psychotic syndromes were significantly more frequent during periods of steroid exposure.

Why are these psychiatric effects rarely reported in the literature? One reason may be that the doses of anabolic steroids routinely used by our subjects were frequently 10–100 times as high as those used in medical studies of these agents. The common practice of "stacking" as many as five or six drugs, including oral preparations, parenteral preparations, veterinary preparations, and other hormones (such as chorionic gonadotropin) may be responsible for psychiatric effects (as well as muscle gains) far beyond those witnessed in research settings. Second, our experience suggests that athletes are wary of revealing their steroid use to physicians. Hence, the psychiatric effects of steroids, although perhaps often witnessed, may rarely be identified as such by professionals. For these reasons, the psychiatric effects of anabolic steroids cannot easily be studied in the laboratory or clinic. Only by observing the effects of these drugs in natural settings, in the doses and combinations actually used by athletes, are we likely to better understand them.

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Some Correlates of Prospectively Defined Premenstrual Syndrome

Paula P. Schnurr, Ph.D.

Correlates of prospectively defined premenstrual syndrome were investigated in 50 women who visited a premenstrual syndrome clinic. To assess premenstrual symptom change relative to daily change, the author used effect size, the difference in mood ratings between the post- and premenstrual phases divided by the standard deviation of the entire cycle. Only 12 women had an effect size greater than or equal to 1.0 in two cycles. The probability of having premenstrual syndrome was positively related to working outside the home and negatively related to age. The results underscore the need to use prospective diagnostic criteria in research on premenstrual syndrome.

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Women who report premenstrual syndrome or who seek treatment for its symptoms differ from those who do not in a number of ways. Of particular interest is a positive association between premenstrual syndrome and affective illness (1) and perhaps even psychiatric illness in general (2). There also appears to be an association between premenstrual syndrome and certain demographic variables; for instance, housewives and women with less education report more premenstrual symptoms than those who are employed and/or better educated (3). In addition, women who complain of premenstrual syndrome experience more menstrual cycle irregularities, such as longer menstrual cycles (4).

Unfortunately, in studies that rely on retrospective self-reports (e.g., 1) or the seeking of treatment (e.g., 2) to indicate the presence of premenstrual syndrome, up to 50% of the subjects may not have premenstrual syndrome as defined by prospective diagnostic criteria (5–7). Such heterogeneity may compromise conclusions regarding both the correlates and the etiology of the disorder. In the only study on correlates of premenstrual syndrome that used prospective diagnostic criteria (8), the women with false premenstrual syndrome were twice as likely as those with actual premenstrual syndrome to have a history of psychiatric disorder. This finding suggests that the association between premenstrual syndrome and psychiatric disorder may be due to women who do not actually have premenstrual syndrome. Other associations may be similarly confounded.

Therefore, I undertook the present study to look at some correlates of prospectively defined premenstrual syndrome. Measures of psychological state and demographic characteristics and one measure of menstrual cycle regularity (cycle length) were used to predict worsening of mood from post- to premenstrual phases. On the basis of previous findings (8), younger women were expected to show greater change than older women. Other predictions were not possible given the lack of similar studies that used prospective symptom assessment.

As in several other studies (6–8), a global measure of mood was used rather than a more detailed symptom measure because virtually all premenstrual syndrome sufferers complain of mood change (6). The choice of a way to assess mood change was difficult because there is still no agreement about what degree of symptom change constitutes premenstrual syndrome. For example, a National Institute of Mental Health panel recommended that the criterion be "marked" symptom change from post- to premenstrual phases (9) but did not include a definition of "marked." Rubinow, Roy-Byrne, and associates (6–8) have used a mood worsening of 30% as a definition of premenstrual syndrome, a measure that is appealing because of the simplicity with which it can be computed. However, this measure does not take intraindividual variability into account, so that an affectively labile woman would be considered to have the same amount of mood change as one who is more stable if both experienced the same mean change.

To avoid this possibility, I used effect size (10) to assess premenstrual symptom change relative to daily change. This is simply the size of the difference between treatments (in an experimental study) or population samples (in a case-control study), usually expressed in dimensionless terms by dividing the difference by the standard deviation of the group means. By

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using effect size to measure premenstrual symptom change, one thus has an index that is standardized relative to a given woman's variability. One still does not have a criterion for deciding when the change is clinically significant. In the present study I used 1.0 as a cutoff point between the groups with and without premenstrual syndrome. This may have been a conservative decision, but conceptually it seemed necessary to require that the post- to premenstrual symptom change be at least as large as the woman's day-to-day variability.

METHOD

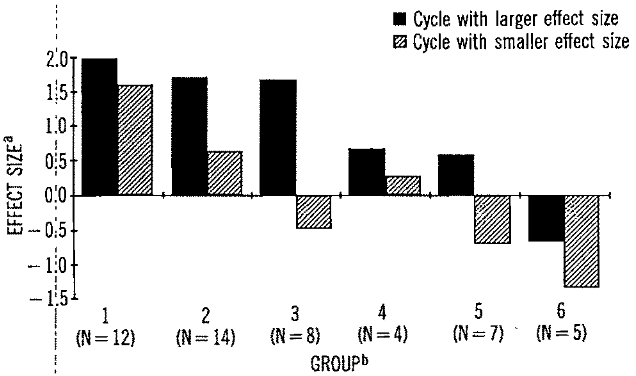
Fifty women were selected as subjects from 83 consecutive patients at a premenstrual syndrome clinic. The reasons for nonselection were failure to return to the clinic after the initial visit ($N=19$), failure to keep records correctly ($N=4$), hysterectomy ($N=2$), and completion of records for one ovulatory cycle only ($N=8$).

At her initial clinic visit, each subject filled out a booklet consisting of a cover sheet that requested demographic information and a short form of the Hopkins Symptom Checklist (11) which included the 25 symptoms from the depression and somatization scales. The subject rated the extent to which she had experienced each of these symptoms during the preceding week on a 5-point scale (0=not at all, 4=extremely). The depression and somatization items were each averaged to yield the subject's scores on these two scales. The demographic information included age, marital status (1=married or cohabitating, 0=not), education level (1=8 years or less, 2=some high school, 3=high school graduate, 4=some college, 5=college graduate, 6=postgraduate degree), and employment (1=working outside the home, 0=housewife).

After the initial visit, the subject began keeping daily records of her basal body temperature upon awakening and ratings of her emotional state on a 9-point scale (1=best ever, 9=worse ever). The ratings were made for at least two cycles to obtain data from two ovulatory cycles for each subject. The temperature charts were reviewed by an obstetrician-gynecologist or one of two gynecological nurse practitioners to determine the probable date of ovulation.

For each subject, the length of each cycle was determined from the daily ratings. The postmenstrual phase was defined as beginning on the day after the cessation of menstruation and lasting for no longer than 6 days but only up to the day before ovulation. The premenstrual phase was defined as the 6 days before menstruation in the following cycle. Premenstrual symptomatology was computed for each cycle as the effect size (10) of mood change from the post- to premenstrual phase. Effect size for each woman was computed as the difference between phases divided by the standard deviation of the entire cycle.

FIGURE 1. Consistency of Premenstrual Mood Change Across Two Cycles in 50 Patients at a Premenstrual Syndrome Clinic



[a] Effect size=(premenstrual phase mean−postmenstrual phase mean)/cycle standard deviation.

[b] Groups were defined on the basis of effect size. Group 1: both cycles, ≥1. Group 2: one cycle, ≥1; one cycle, >0. Group 3: one cycle, ≥1; one cycle, ≤0. Group 4: both cycles, <1 and >0. Group 5: one cycle, <1 and >0; one cycle, ≤0. Group 6: both cycles, ≤0.

RESULTS

The mean±SD effect size for premenstrual change was 0.88±1.12 in cycle 1 and 0.67±1.06 in cycle 2. Twelve women (24%) had an effect size greater than or equal to 1.0 in both cycles (see figure 1). These women were considered to have premenstrual syndrome for the purpose of the analyses that follow. As can be seen from figure 1, most of the remaining women varied in their reports of premenstrual worsening from cycle to cycle, and five (10%) reported consistent premenstrual improvement. Across both cycles, the group with premenstrual syndrome had a mean±SD effect size of 1.77±0.29 and the group without premenstrual syndrome had an effect size of 0.46±0.78 ($t=8.58$, $df=46.7$, $p<0.001$; t test corrected for inequality of group variances).

Data from the two Hopkins Symptom Checklist scales, the four demographic variables, and average cycle length are displayed in table 1. Univariate tests revealed differences between the groups on two variables. The premenstrual syndrome group was younger than the group without premenstrual syndrome ($t=2.92$, $df=49$, $p<0.01$). The premenstrual syndrome group also had a higher mean score on the Hopkins Symptom Checklist depression scale ($t=2.28$, $df=49$, $p<0.05$).

Stepwise logistic regression was chosen to explore the unique contribution of each variable in predicting premenstrual syndrome, which was coded as 1=premenstrual syndrome and 0=no premenstrual syndrome. The p values for entry and removal of terms were set at 0.10. Because phase at initial visit, when the Hopkins Symptom Checklist was completed, was not controlled, phase was forced into the regression as a covariate before the stepping procedure. The stepwise procedure selected two variables, age (standardized

TABLE 1. Description of 50 Women With or Without Premenstrual Syndrome

Group	Age (years)[a]		Housewife		Married		College Diploma		Hopkins Symptom Checklist Score				Cycle Length (days)	
									Depression[b]		Somatization			
	Mean	SD	N	%	N	%	N	%	Mean	SD	Mean	SD	Mean	SD
Premenstrual syndrome (N=12)	29.2	6.0	4	33	8	67	7	58	2.35	0.69	1.11	0.61	28.6	4.2
No premenstrual syndrome (N=38)	35.4	6.5	16	42	25	66	12	32	1.77	0.97	1.24	0.91	27.9	4.4

[a] $t=2.92$, df=49, $p<0.01$.
[b] $t=2.28$, df=49, $p<0.05$.

logistic regression coefficient=-2.42, $\chi^2=6.84$, df=1, $p<0.01$; goodness-of-fit $\chi^2=41.98$, df=46, n.s.) and employment status (standardized logistic regression coefficient=1.78, $\chi^2=3.85$, df=1, $p=0.05$; goodness-of-fit $\chi^2=38.13$, df=45, n.s.). Premenstrual syndrome was more likely among younger women and among those who worked outside the home. Depression failed to predict premenstrual syndrome when the phase during which it was measured was taken into account. Attempts to fit alternative models showed that no other terms could be added. Also, a stepwise ordinary least squares regression predicting effect size as a continuous variable selected only age and employment as predictors.

DISCUSSION

In this prospective study, age and employment status predicted premenstrual syndrome. Marital status, education level, depression and somatization scores, and cycle length did not uniquely contribute to predicting premenstrual syndrome. The increased likelihood of premenstrual syndrome in women working outside the home contrasts with Friedman and Jaffe's observation (3) of the highest symptom levels among housewives. Similarly, the increased likelihood seen in younger women here and by DeJong et al. (8) contradicts Logue and Moos' contention (12) that the reporting of premenstrual symptoms increases with age—but not Woods et al's finding (4) of a negative relationship between premenstrual depression and age. One explanation for these discrepancies is differences between retrospective and prospective methods.

Only one-quarter of the women studied had consistently severe premenstrual syndrome. Of those who did not, almost half had at least 1 month in which mood improved premenstrually, although none of these women subjectively reported the improvement. For example, one woman with asthma who was hospitalized for respiratory distress on day 6 of a 25-day cycle recalled the event as indicating premenstrual difficulties. Why this woman and so many others inaccurately believe they have premenstrual syndrome cannot be determined from the present study. Because most of them are likely to have a history of psychiatric disorder (8), it may be that they are searching for a more socially acceptable, medical explanation for their symptoms. Why older women and housewives are more likely to describe variations in their affective state as premenstrual syndrome in the absence of the necessary symptom pattern also cannot be determined from this study. Nevertheless, the decreased likelihood of premenstrual syndrome in such women may be useful in interpreting complaints of premenstrual syndrome in a clinical setting. Age may be given special consideration, as 75% of the group with premenstrual syndrome but only 24% of the group without it was under 30.

The effect size of mood change from the post- to the premenstrual phase was used to measure premenstrual syndrome. One advantage of using effect size is that it provides a measure of premenstrually related change relative to the day-to-day change a woman is likely to experience. Another is that it is dimensionless, like a Z score, a property that is desirable for interindividual comparisons. In addition, it suggests a conceptually meaningful cutoff point for deciding when a given woman has premenstrual syndrome, namely, when variability due to premenstrual syndrome is greater than day-to-day variability. One disadvantage associated with the use of effect size is that it requires calculations which are somewhat cumbersome to perform without a scientific calculator or computer. The 30% change score used by Rubinow, Roy-Byrne, and their colleagues (6–8) may be simpler for the clinician who has a single patient with premenstrual syndrome. Another disadvantage is that the method used here, like the 30% change method, ignores the within-subjects (paired) nature of the post-premenstrual comparison. Although it is possible to compute an effect size for a within-subjects comparison, there does not seem to be a logical basis for doing so in the present context; i.e., how could one pair days of the post- and premenstrual phases in the same way that one would pair responses to different treatments in a crossover design?

The results of this study underscore the need to use prospective diagnostic criteria in future research on premenstrual syndrome. It will not be possible to discover its medical, psychological, and demographic correlates—much less its etiology—without careful definition of study samples. The results also highlight the need to rely on prospective measurement in a clinical setting. Treatment must depend on whether the temporal pattern of symptom change in a given woman suggests premenstrual syndrome or another disorder.

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Behaviors and Attitudes Related to Eating Disorders in Homosexual Male College Students

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To investigate whether homosexuality predisposes males to eating disorders, the authors studied 48 nonpatient homosexual male students at UCLA. The homosexual men had higher prevalences of binge-eating problems, of feeling fat in spite of others' perceptions, of feeling terrified of being fat, and of having used diuretics than other male students. They also scored higher on the Eating Disorders Inventory scales for drive for thinness, interoceptive awareness, bulimia, body dissatisfaction, maturity fears, and ineffectiveness. One of the 48 homosexual men and one of the 300 comparison group men met criteria for probable past histories of eating disorders.

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Several reports (1–3) have described high prevalences (up to 50%) of homosexual conflict in male patients with anorexia nervosa, and two other reports have described a higher than expected rate of homosexual behaviors among male patients with eating disorders. Herzog et al. (4) reported that 26% (seven of 27) of their male patients with eating disorders were homosexual, five of whom had conflicts about their sexuality. Fichter and Daser (5) reported that among their male anorexia nervosa patients for whom such data were available, 25% (five of 20) had experienced some homosexual contact and 50% (five of 10) viewed themselves as less masculine than others; three of their four male patients with atypical eating disorders had frequent homosexual behaviors. They also found a high prevalence of "superfeminine" scores among their male patients with eating disorders on the masculinity-femininity scale of the Freiburger Personality Inventory, and 13 of the 20 patients interviewed reported a childhood (before illness) preference for such activities as cooking, sewing, and other atypical traditionally defined gender role behaviors. Averaging 19 years of age at the time of their interviews, four said they would prefer being a girl and 14 had never or only rarely been in love with a girl. Based on Green's observations that effeminate boys are more likely than others to become homosexual adults (6), Fichter and Daser (5) speculated that "normal uncomplicated psychosexual development may well be incompatible with anorexia nervosa in the male."

In contrast to these studies, Pope et al. (7) found only one (6.7%) of their 15 male patients with bulimia to be homosexual, and Mitchell and Goff (8) did not mention homosexuality in their study of 12 male patients with bulimia (although the occupations of that group included a secretary, a nurse, and a nurse's aid—jobs that are traditionally held by women).

Although homosexual men may be more likely than heterosexual men to develop eating disorders because of possible excessive concern with slim bodies and other attitudes traditionally associated with women, to our knowledge, no study has reported on behaviors and attitudes related to eating disorders in a nonclinical sample of homosexual men. As part of a larger study of such behaviors and attitudes among various student groups at the University of California at Los Angeles (UCLA), we studied a group of homosexual men.

METHOD

Homosexual men who were attending a monthly meeting of the Gay Men's Rap Group at UCLA were asked to complete questionnaires that requested information about their demographics, degree of homosexuality, and attitudes and behaviors associated with eating disorders. The items related to eating disorders were compatible with diagnostic criteria from *DSM-III*. We obtained a male comparison group by distributing similar questionnaires (excluding questions on homosexuality) to a large class of students enrolled in an undergraduate abnormal psychology course, to members of several male athletic teams at UCLA, to undergraduate men majoring in dance, and to sequential samples of male students who used the Student Health Service primary care clinic for general medical

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TABLE 1. Bulimic Attitudes and Behaviors of Homosexual Male Students and Male Comparison Groups From UCLA[a]

			Male Comparison Group									
	Homosexual Men (N=48)		Total (N=300)		Primary Care Attenders (N=120)		Psychology Class Students (N=59)		Dance Majors (N=10)		Athletes (N=111)	
Present or Past Problem	N	%	N	%	N	%	N	%	N	%	N	%
Binge eating	6	12.5[b]	12	4.0[b]	6	5.0	1	1.7	1	10.0	4	3.7
Self-induced vomiting	3	6.4	12	4.3	6	5.4	2	3.6	1	10.0	3	3.0
Laxative use to control weight	2	5.6	4	1.8	0	0.0	2	4.2	0	0.0	2	2.7
Diuretic use to control weight	4	11.4[c]	6	2.7[c]	5	5.4	0	0.0	0	0.0	1	1.4
Excessive deliberate weight loss	3	6.3	8	2.7	1	0.8	5	8.5	0	0.0	2	1.8
Overactivity without enjoyment	6	12.5	25	8.3	9	7.5	6	10.2	2	20.0	8	7.2
Feeling terrified of being fat	7	14.6[d]	13	4.3[d]	7	5.8	3	5.1	1	10.0	2	1.8
Feeling fat despite others' perceptions	12	25.0[e]	29	9.7[e]	15	12.5	5	8.5	4	40.0	5	4.5
Feeling obsessed with thoughts of food	5	10.4	16	5.3	9	7.5	1	1.7	2	20.0	4	3.6

[a] The N on which some percents are based differs because of missing data.
[b] $\chi^2=5.94$, df=1, p=0.02.
[c] $\chi^2=6.24$, df=1, p=0.01.
[d] $\chi^2=8.03$, df=1, p=0.005.
[e] $\chi^2=9.36$, df=1, p=0.002.

complaints during a 1-month period. All respondents also completed the Eating Disorders Inventory of Garner et al. (9). Statistical analyses compared two groups of respondents: the homosexual men and all the men in the male comparison group. Categorical variables were analyzed with chi-square analysis. Continuous variables were analyzed with two-tailed t tests. For historical comparison, we also examined the scores of a male comparison group of 166 first- and second-year undergraduate students at the University of Toronto published by Garner et al. (9), but we performed no statistical comparisons.

RESULTS

Questionnaires were returned by 48 (98%) of 49 homosexual men and by 120 students who attended the Student Health Service, 111 athletic team members (track and field, water polo, swimming, gymnastics, and soccer teams), 59 psychology students, and 10 students majoring in dance (a 59%–90% return rate). The mean±SD age of all respondents was 21.6 ± 4.0 years (22.2 ± 3.3 years for the homosexual men); their mean±SD weight as a percentage of the 1983 Metropolitan Life Insurance tables of recommended weight for height was 100%±12% (100%±14% for the homosexual men); their desired weight in relation to height was 102%±9% of that recommended (98%±6% for the homosexual men); their highest past adult weight was 105%±14% of that recommended (105%±18% for the homosexual men), and their lowest past weight as adults was 93%±12% of that recommended (92%±14% for the homosexual men). About three-quarters of the respondents were undergraduates and the rest were first- and second-year graduate students. The ethnic distribution of the respondents was 73% Caucasian, 11% Hispanic, 8% black, and 8% Asian-American.

Table 1 presents data on students from each group who reported present or past eating behaviors and attitudes commonly associated with anorexia nervosa or bulimia. According to simulated diagnosis based on *DSM-III* criteria by a method reported elsewhere (10), only one of the homosexual men would have ever met criteria for a past diagnosis of bulimia, and only one (an undergraduate dance major) of the 300 other male students would have met criteria for a past diagnosis of anorexia nervosa. The prevalence of these behaviors reported by the other nine dance majors was not higher than that for the other comparison groups. The homosexual men were significantly more likely than the men in the comparison group to report a present or past problem with binge eating, use of diuretics, feeling terrified of being fat, and feeling fat despite others' perceptions.

Table 2 lists the Eating Disorders Inventory scale scores for each of the male student groups and also for Garner et al.'s male comparison group (9). Scores were higher for the homosexual men than for our male comparison group on drive for thinness, interoceptive awareness, bulimia, body dissatisfaction, ineffectiveness, maturity fears, and the total scale.

Only 6.3% (N=3) of the homosexual men described themselves as bisexual, whereas 39.6% (N=19) described themselves as predominantly homosexual and 54.2% (N=26) as exclusively homosexual. No differences were found between the 26 exclusively homosexual men and the 22 others regarding behaviors or attitudes related to eating disorders or scores on the Eating Disorders Inventory.

DISCUSSION

Several limitations in the design of this study caution against generalizing these findings to the larger homosexual male community. First, the sample consists

TABLE 2. Eating Disorder Inventory Scores of Homosexual Male College Students and Male Comparison Groups

	UCLA Homosexual Men (N=48)		UCLA Male Comparison Group										University of Toronto Male Comparison Group (9) (N=166)	
			Total (N=300)		Primary Care Attenders (N=120)		Psychology Class Students (N=59)		Dance Majors (N=10)		Athletes (N=111)			
Scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drive for thinness	4.0[a]	4.0	2.7[a]	2.2	2.7	2.1	2.5	2.1	2.2	2.3	2.8	2.3	1.6	0.2
Interpersonal distrust	2.0	3.1	2.1	3.0	1.8	2.3	2.8	4.0	1.5	2.2	2.2	2.9	3.1	0.2
Interoceptive awareness	2.5[b]	4.0	1.1[b]	2.0	1.1	1.8	1.4	2.5	0.5	0.8	1.0	1.9	1.4	0.4
Bulimia	1.3[c]	2.4	0.6[c]	1.2	0.7	1.3	0.5	1.1	0.5	0.8	0.6	1.2	1.0	0.1
Body dissatisfaction	5.4[d]	5.8	3.2[d]	3.8	3.6	4.0	2.8	3.6	3.9	3.1	2.8	3.8	3.9	0.4
Ineffectiveness	2.9[e]	5.3	1.0[e]	2.2	1.0	1.6	1.5	3.8	0.4	0.7	0.7	1.8	1.6	0.2
Maturity fears	4.1[f]	2.4	3.2[f]	2.1	3.5	2.5	3.3	2.2	3.9	2.2	2.7	1.6	2.7	0.4
Perfectionism	7.0	4.3	6.8	3.9	7.2	3.9	6.2	3.9	4.4	2.2	6.8	3.9	6.2	0.3
Total score	29.3[g]	23.6	20.5[g]	11.2	21.3	11.0	21.2	13.2	17.3	7.0	19.6	10.4	—	

[a] t=2.32, df=51.6, p=0.02, assuming unequal variances.
[b] t=2.30, df=49.5, p=0.03, assuming unequal variances.
[c] t=2.03, df=50.9, p=0.05, assuming unequal variances.
[d] t=2.54, df=52.4, p=0.01, assuming unequal variances.
[e] t=2.46, df=49.8, p=0.02, assuming unequal variances.
[f] t=2.61, df=339, p=0.009, assuming equal variances.
[g] t=2.51, df=49.4, p=0.02, assuming unequal variances.

entirely of college students. Second, the sample is one of convenience, not one drawn from the entire male homosexual student body. However, the response rate of 98% among those solicited suggests that these findings may be representative of students who attend homosexual rap groups. Third, this is a cross-sectional, noninterview study. The study cannot answer whether those students with relatively elevated Eating Disorders Inventory scale scores are in fact at risk to develop clinical eating disorders. As a group they still fall within the age at risk, and some may develop clinical syndromes at a later date. Fourth, the nonhomosexual students were not asked about sexual life style, so that group may include some students who would identify themselves as homosexuals; however, this would make the differences reported more conservative than if the comparison group members all reported a heterosexual life style.

The fact that there were no wrestlers in the athletic comparison group may have contributed to the low prevalence of self-reported purging behaviors in this group. At least anecdotally, the prevalence of "instrumental" purging, i.e., self-induced vomiting or diuretic and/or laxative use with the specific purpose of reducing weight before competitions, is reported to be high among some male athletes, particularly wrestlers and jockeys; however, those behaviors should not be equated with clinical bulimia nervosa.

At this point, explanations for our finding of a higher prevalence of behaviors and attitudes related to eating disorders among male homosexuals must remain speculative. These findings may represent the cultural shapings of self-identifications that for at least some homosexual males tend toward the effeminate from an early age (6). Nevertheless, these findings suggest that among some homosexual male college students, behaviors and attitudes related to eating disorders are those which would be expected if these homosexual men were at greater risk for eating disorders. On the basis of these findings, larger community-based prospective studies are warranted.

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Weaning and Depression: Another Postpartum Complication

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The dramatic endocrinologic changes that occur after childbirth and the coincident affective disturbances that range from "maternity blues" to major depression have stimulated much theorizing and some study. The role of breast-feeding and weaning has received remarkably little attention both in the more biologically oriented studies and in epidemiologic work. This paper reviews endocrinologic data which support the thesis that postpartum psychiatric disorders have a hormonal basis and discusses the possible psychiatric effects of breast-feeding and weaning. The cases of four patients who developed major depressions in close temporal association with weaning are presented and discussed.

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In spite of the interest in possible links between puerperal endocrinologic changes and postpartum psychiatric disorders, little attention has been paid to the roles of breast-feeding and weaning. The presence or absence of breast-feeding did not correlate with the development of the early-occurring "maternity blues" syndrome in a number of studies (1–5). This finding may not reveal much about the psychobiology of breast-feeding, however, because prolactin levels are quite high in the immediate postpartum period regardless of whether breast-feeding is initiated or not. Similarly, estrogen and progesterone levels precipitously decrease in all postpartum women. In his well-known and respected epidemiologic review of puerperal mental illness, Paffenbarger (6) found that there was no correlation between breast-feeding and the development of psychiatric disorders. No correlation between breast-feeding and later-occurring postpartum depression was identified in a study by Cox et al. (4).

Two studies did find that breast-feeding women were at higher risk for postpartum depression. Although the difference narrowly missed statistical significance, data reported by Dalton (7) indicated that women who were breast-feeding 2 weeks after giving birth were more depressed than those who were not. This finding was limited by the lack of clarity and precision in the diagnosis of depression in these women. More compelling and cogently argued is a report by Adler and Cox (8). They divided breast-feeding women into two groups: 1) those who were exclusively breast-feeding and who presumably were the most likely to have a plasma endocrine profile of elevated prolactin and suppressed estrogen and progesterone and 2) those who were partially breast-feeding and who had begun supplementing their babies' diets with solid foods. Those who were breast-feeding exclusively had a significantly higher prevalence of postpartum depression at 3–5 months. The investigators acknowledged that the demands of exclusive breast-feeding and the possibility that those who breast-feed exclusively are a self-selected group of depression-prone women could have contributed to these findings. However, Adler and Cox refined their findings even further by adding data about which women were using oral contraceptives. Overall, depression proved to be significantly less prevalent among the women who were most likely to have normal plasma levels of endogenous hormones.

We found no endocrinologic or epidemiologic studies that dealt with a possible relationship between weaning and postpartum depression. The reports that follow describe episodes of major depression which developed in four women within 2 weeks after they had begun to wean their infants.

CASE REPORTS

Case 1. Ms. A, a 25-year-old primiparous married white woman, had an uncomplicated vaginal delivery of a normal girl at term. Her early postpartum course included anxiety and crying, which her obstetrician and she considered normal. She weaned the baby at 6 months of age and within 2 weeks developed symptoms of depression, including insomnia with early morning awakening, crying, anxiety, and fears of being alone. She felt unable to care for her child and developed paranoid ideation and religious preoccupations. Her menses resumed 7 months after the birth of the child. Her husband reported that her symptoms worsened during each menstrual period. She was admitted to the hospital 10 months after the birth and was treated with nortriptyline, up to 100 mg/day, with serum levels in the therapeutic range. After an early positive response to the medication, she abruptly became confused, hypersexual, and agitated. The

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nortriptyline was discontinued, and she improved on a regimen of lithium and haloperidol.

A sister of Ms. A had a history of postpartum depression requiring hospitalization. Ms. A's own history did not include any psychiatric disturbance. Her medical workup, including thyroid function tests, yielded normal findings.

Case 2. Ms. B, a 27-year-old married white woman, delivered her first child, a healthy boy. The birth and postpartum period were uneventful until a severe upper respiratory infection prompted her to precipitously wean him at 7 months of age. She developed a psychotic depression within 2 weeks. She became morose, had delusions of guilt, stayed in bed while relinquishing the baby's care to her extended family, and had decreased appetite, weight, and sleep. She had experienced irregular menses over the previous 3 months. Her family doctor prescribed a tricyclic antidepressant, which she took irregularly, and she improved within 3 months.

Ms. B was admitted to the hospital 2 years later, 9 months after the birth of her second son. Within weeks of his birth, she was delusionally preoccupied with her health and the health of the baby, believing they had been infected and possibly mutilated during the delivery. She stopped breast-feeding this child at approximately the same time her symptoms began because her milk supply was inadequate and the baby was not gaining weight. A trial of outpatient treatment with doxepin alone had failed. She also failed to respond to combined nortriptyline and haloperidol treatment in the hospital and chose to be transferred to a facility nearer her home for ECT.

An older sister of Ms. B had had an episode of major depression not associated with childbirth. Another sister and the mother were alcoholics. Ms. B had abused alcohol and drugs during late adolescence and had made two suicide gestures, while intoxicated, in response to breakups of romances. Medical and gynecological evaluations of Ms. B revealed no abnormalities.

Case 3. Ms. C, a 28-year-old primiparous married white woman, had a pregnancy complicated by the development of herpes zoster at 37 weeks of gestation and preclampsia at 38 weeks. Labor was induced at 39 weeks, and a healthy female infant was delivered with high forceps. During the first postpartum week, Ms. C described feeling emotionally labile but happy. She later felt ambivalent about returning to work but, in anticipation of doing so, she began weaning her daughter at 4 months of age. Within 2 weeks of starting partial breast-feeding, she became anxious, sad, and tearful; she experienced feelings of guilt and inadequacy and decreased concentration. She stopped breast-feeding entirely 1 month into the weaning period in order to begin a course of amitriptyline treatment. Side effects prompted her to discontinue the medication after 7 days. Her depression worsened, and she developed the delusional conviction that her poor mothering had caused the child irreparable emotional damage. Convinced that she and the child would be "better off" without each other, she began a series of destructive behaviors toward the child, including giving her plastic bags to play with and covering her face with a pillow.

Ms. C signed out against medical advice after she had been hospitalized for only 1 day 5½ months after the birth, but she continued these behaviors for 2 more weeks. While another hospitalization was being arranged, she suffocated the baby. The patient was admitted to our facility and improved dramatically with six bilateral ECTs. She was then started on a regimen of nortriptyline for prophylaxis. Medical evaluation revealed no abnormalities. She had experienced one day of painless vaginal bleeding 1 week after beginning to wean the baby, and menses had not resumed by the time of her hospital discharge 7½ months after the birth of the baby.

Ms. C's mother had had a postpartum depression and had made a suicide attempt after the birth of the patient's younger twin brothers, for which she was treated with ECT. The maternal grandmother was an alcoholic. The patient had had a 6-month episode of anorexia nervosa at age 13, which had responded well to a behavior therapy program.

Case 4. Ms. D, a 36-year-old married white woman, had not breast-fed either of her first two children, who were boys. She had not planned to breast-feed the first, and her hopes of doing so with the second were ended when he was born 6 weeks prematurely. One month after the second birth, she developed a "moderate depression," which gradually responded to outpatient psychotherapy. Her third child, a daughter, was breast-fed successfully and without a relief bottle for 6 months. Ms. D, who always felt happiest during her pregnancies, continued "to feel wonderful" during these 6 months and particularly savored the breast-feeding experience itself. However, within several days of weaning the baby, she abruptly began to experience marked feelings of depression and anxiety, frequent tearfulness, insomnia, agitation, severe anorexia, great difficulty in concentrating, palpitations, headaches, "pins and needles" throughout her body, "hot flashes," and anhedonia. The patient attributed this to the weaning and, on her own, attempted to resume breast-feeding the baby at least a few times a day.

She contacted her therapist, who referred her to a psychiatrist for pharmacotherapy; however, both patient and psychiatrist were reluctant to institute pharmacological treatment because of the resumption of breast-feeding. Ms. D experienced a gradual improvement in her symptoms within 2 weeks of resuming breast-feeding and then attempted a more gradual weaning in conjunction with ongoing outpatient psychotherapy. Over the 3-month period following the resumption of partial breast-feeding, her symptoms gradually abated. One month after completing weaning, she experienced her first period since becoming pregnant.

Ms. D was adopted, and nothing was known of her biological parents; her adoptive family had no known psychiatric history. The patient had had periodic bouts of depression with anxiety since childhood, for which she had received outpatient psychotherapy and occasional benzodiazepines. She had never been hospitalized. She also gave a history of marked irritability and mood lability every month during the premenstrual phase of her cycle.

DISCUSSION

Endocrinologic studies linking disturbances of mood and behavior to the hormonal changes of the puerperium are largely confined to the first postpartum week. Some data support a correlation between hormonal changes and maternity blues. This syndrome is a common, mild disorder characterized by emotional lability and tearfulness, and possibly including irritability, sleep disturbance, and confusion, that occurs during the first postpartum days. Sharp decreases in estrogen and progesterone accompanied by elevated levels of prolactin also occur during these first few postpartum days. Nott et al. (5) found no clear correlation between observed postpartum hormonal changes and the development of maternity blues. They did find some weak associations between irritability and a high predelivery plasma estrogen level, between sleep disturbance and a low postpartum estrogen level, and between self-reports of depression 10 days after giving birth and a proportionally greater decrease in plasma progesterone level.

Carroll and Steiner (9) reviewed premenstrual syndromes in 1978 and underscored the similar endocrinologic profiles that occur during the postpartum period and in premenstrual syndromes. They cited evidence for a high plasma prolactin level and a low plasma estrogen level in premenstrual depression and a high plasma prolactin level and a low plasma progesterone level relating to premenstrual irritability. However, their group later failed to demonstrate a relationship between an elevated prolactin level and premenstrual syndromes (10). Nonetheless, as stressed by de la Fuente and Rosenbaum (11), there is heuristic value in Carroll and Steiner's original model (9) insofar as it illustrates how the multiple and interrelated endocrinologic changes involved in premenstrual syndromes or postpartum disorders may be associated with wide variations in mood and behavior. Other studies of prolactin and mood in the postpartum period include that of George et al. (1), who found a correlation between plasma prolactin level and anxiety, tension, and depression, and that of Mastrogiacomo et al. (12), who found a relationship between an elevated plasma prolactin level and hostility.

The question of whether a correlation exists between maternity blues with its attendant hormonal profile and the development of postpartum depression has not been carefully studied. Handley et al. (13) found a correlation between excessively high cortisol levels at 38 weeks of gestation, and on the fifth postpartum day, and both maternity blues and later clinical depression. They also reported a significant decrease in free plasma tryptophan on the third postpartum day in maternity blues patients and an absence of the normal peaking of total tryptophan on the second postpartum day in patients who had become depressed within 6 months after giving birth. Researchers at the University of Edinburgh found that the development of maternity blues predisposed to the development of postpartum depression (3, 4).

It is interesting to observe that three of our patients had family histories of affective disorder, and two had first-degree relatives who suffered postpartum illnesses; because of early adoption, family data were not available for the fourth patient. Additionally, there are enough available data to indicate that two of these patients had maternity blues. The patient in case 1 had exacerbations of her disorder with her menses, and those in cases 2, 3, and 4 had not resumed regular menstrual cycles. This provides suggestive support for the proposal of Adler and Cox (8) that women with the endocrinologic profile of high plasma levels of prolactin and decreased levels of estrogen and progesterone are at greater risk for developing depression. Weaning sets the stage for a return to normal endocrinologic functioning, and significant hormonal changes occur during the process. It is useful to recall Smith's (14) cautioning against the overly simplified, reductionistic view that the absolute amount of one or more hormones could account for mood disturbances. He pointed out that the relative and changing amounts of several hormones and the ratios of the various subtypes of estrogen, for example, have not been adequately studied. Thus, it is possible that as-yet unidentified hormonal patterns or changes in previously stable patterns may contribute to the development of any or all of the disorders we have discussed. The sequence of hormonal readjustments that also follows weaning may be causally related to the rapid onset of the depressions presented here.

The most parsimonious explanation for the striking occurrences in these cases would suggest a mix of biologic and psychodynamic factors. The endocrine patterns and changes characteristic of both breastfeeding and weaning might have predisposed this group of genetically vulnerable women to major depression. The symbolic meaning of weaning, which could include the loss of the early symbiotic bond between mother and baby, might elicit feelings of sadness and guilt that then serve as a psychological stressor sufficient to precipitate the depression that follows. Prospective clinical and endocrine studies of nursing mothers, comparing those with and those without personal or family histories of affective disorder, would clearly be helpful in investigating this proposed model for women who become depressed when they wean their infants.

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Refining Prevalence Estimates of Pathological Gambling

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Pathological gambling was officially defined as a psychiatric illness by APA in 1980. The authors report on the results of a state-wide study in New York that indicated significant differences between problem gamblers in the general population and pathological gamblers entering publicly funded treatment programs. These results, based on telephone interviews using standardized assessment instruments with 1,000 persons, raise serious clinical and programmatic issues regarding the development and organization of appropriate services for pathological gamblers. They also point to the fact that large segments of the general population are not receiving needed services.

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Pathological gambling was first included as a diagnosable mental disorder in *DSM-III* in 1980. Classed as a disorder of impulse control, pathological gambling was defined in *DSM-III* as "a chronic and progressive failure to resist impulses to gamble." The diagnostic criteria reflected then prevailing assumptions about the nature of pathological gambling. According to *DSM-III,* pathological gambling compromises, disrupts, or damages family, personal, and vocational pursuits, as indicated by the presence of at least three of the following seven items: 1) arrest for forgery, fraud, embezzlement, or income tax evasion due to attempts to obtain money for gambling, 2) default on debts or other financial responsibilities, 3) disrupted family or spouse relationship due to gambling, 4) borrowing of money from illegal sources (loan sharks), 5) inability to account for loss of money or to produce evidence of winning money, if this is claimed, 6) loss of work due to absenteeism in order to pursue gambling activity, 7) necessity for another person to provide money to relieve a desperate financial situation (p. 292).

The criteria for pathological gambling have been changed in *DSM-III-R* to emphasize physiological symptoms such as tolerance and withdrawal. The data collected in the study reported here are based on *DSM-III* criteria.

Public and private programs offering education, outreach, and counseling for pathological gamblers have expanded rapidly since 1980. State-funded mental health services have been developed for pathological gamblers in a number of states, including Connecticut, Maryland, New Jersey, New York, and Pennsylvania, and are being planned in Iowa, Delaware, and Massachusetts. Private sector treatment programs, which in addition to Veterans' Administration (VA) programs were the only available inpatient services before 1980, have remained active but relatively stable in size. Until recently, there have been no data on either the current or lifetime prevalence of pathological gambling in the general population.

This paper reports on a state-wide survey of the current prevalence of pathological gambling in the adult population of New York. The results of this survey indicate that a substantial proportion of the state's population experiences problems with gambling. When these prevalence data are matched with information drawn from our evaluation of compulsive gambling treatment programs in New York State, treatment and prevalence data from a single geographic area can be compared, to our knowledge, for the first time. This comparison raises serious clinical and programmatic issues regarding the development, organization, and distribution of appropriate services for pathological gamblers.

METHOD

The prevalence survey was developed as part of our evaluation of compulsive gambling treatment programs in New York State. The South Oaks Gambling Screen (1) was adapted for use in a telephone survey. This gambling screen is a 20-item scale derived from *DSM-III* criteria. Respondents scoring 3 or 4 points are classified as problem gamblers. Respondents scoring 5 or more points are classified as probable pathological gamblers.

In developing the South Oaks Gambling Screen, Lesieur and Blume (1) subjected a large pool of variables to discriminant analysis. They cross-tabulated scores on this instrument with assessments of independent counselors. The scoring system was carefully

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developed to reduce the number of false-negative and false-positive cases. For our telephone survey, several questions on wagering activities and demographics were added. The instrument was also translated into Spanish for interviewing Hispanic respondents.

Respondents were contacted and interviewed by Fact Finders, Inc., a survey research firm experienced in telephone surveys. Several methods were used to ensure that the survey sample closely matched characteristics of the adult population of New York State. Respondents were randomly selected by using computer-generated telephone numbers, and the entire sample was stratified to proportionally represent the counties of New York on the basis of 1980 census figures. To complete 1,000 interviews, 1,547 contacts were required. The response rate of 65% is comparable to the response rate in telephone surveys on other topics conducted in New York. Forty-three (4.3%) of the 1,000 successfully completed interviews were conducted in Spanish.

Comparison of the demographics of the survey sample with the demographics of the New York State population indicates that there were no significant differences (determined by proportional t test analysis) between the sample and the 1980 state-wide census figures for sex, age, or ethnicity. The lowest education levels were somewhat underrepresented in the survey sample, a result consistent with most survey research. The statistical error associated with the overall sample ranged from 1.9% to 3.1% (95% confidence level).

RESULTS

Twenty-eight of the New York State respondents (2.8% of the sample) obtained scores of 3 or 4 on the South Oaks Gambling Screen. According to the scale used in this instrument, these respondents were classified as problem gamblers. Another 14 of the respondents (1.4% of the sample) scored 5 or more; these respondents were classified as probable pathological gamblers. Based on these findings, we estimate that between 230,000 and 486,400 of New York's 12.8 million adults can be classified as problem gamblers. An additional 89,600 to 269,800 adults can be classified as probable pathological gamblers.

The prevalence of pathological gambling found in this study is consistent with prevalence data from elsewhere in the United States (2; unpublished data of Culleton; unpublished data of Culleton and Lang; unpublished data of the Minnesota Department of Human Services). The results from these previous studies are difficult to compare with the New York study. Different scales were used in each study and different behaviors were taken as indicative of problem gambling. In addition, the categories used to group respondents in these surveys were not comparable. In spite of these drawbacks, the consistency of the results from these surveys is surprising.

Among the 1,000 respondents surveyed in our study, significant differences ($p<0.05$, determined by chi-square analysis) between the sample as a whole and the respondents classified as problem and probable pathological gamblers were found on several dimensions. In reporting the results of the survey, we have combined the responses of those who scored as problem gamblers and those who scored as probable pathological gamblers. This approach is based on our concern with determining differences between respondents without gambling problems and respondents with moderate to severe gambling problems. In calculating the degrees of freedom for the results reported here, we used three age groups (18–29 years, 30–49 years, and 50 or more years) and five income groups ($15,000 or less, $15,001–25,000, $25,001–35,000, $35,001–50,000, $50,001 or more). The calculations for sex, ethnicity, education, and employment were based on dichotomous variables.

Men constituted 44% (N=440) of all respondents but 64% (N=27) of the problem and probable pathological gamblers ($\chi^2=6.49$, df=1, $p=0.01$).

Although 22% (N=220) of the entire sample was under the age of 30, 38% (N=16) of the problem and probable pathological gamblers were in this age group ($\chi^2=8.81$, df=2, $p=0.01$).

Although 23% (N=230) of the entire sample was nonwhite, 43% (N=18) of the problem and probable pathological gamblers were nonwhite ($\chi^2=8.86$. df=1, $p<0.01$).

Problem and probable pathological gamblers were also overrepresented among those earning $25,000 or less. Although 45% (N=450) of the total sample earned $25,000 or less each year, 60% (N=25) of the problem and probable pathological gamblers earned $25,000 or less each year ($\chi^2=14.13$, df=4, $p<0.01$).

Although 18% (N=180) of the total sample had not graduated from high school, 33% (N=14) of the problem and probable pathological gamblers had not graduated from high school ($\chi^2=6.81$, df=1, $p<0.01$).

Although 7% (N=70) of the entire sample was unemployed, 21% (N=9) of the problem and probable pathological gamblers was unemployed at the time the survey was done ($\chi^2=13.62$, df=1, $p<0.01$).

There were regional differences in the distribution of respondents in the total sample compared with respondents in the diagnostic categories. Although 42% (N=420) of the entire sample resided in the New York City region, 55% (N=23) of the problem and probable pathological gamblers resided in the New York City region.

There was an apparent correspondence between the rate of respondents who scored 5 or more points on the diagnostic scale (1.4%) and the rate of respondents who agreed with the statement, "Do you feel you have ever had a problem with gambling?" (1.6%). When the correspondence was tested, however, these two groups proved not to be identical. Only 14% (N=4) of the problem gamblers and 36% (N=5) of the probable pathological gamblers felt that they had ever had a problem with gambling.

SURVEY RESULTS COMPARED WITH TREATMENT PROGRAM DATA

In 1982, two demonstration programs for the treatment of pathological gamblers and their families were opened in New York State. One of the programs was located on Staten Island and the other was located in Rochester. A third program in Manhattan was opened in 1985. As part of our evaluation of the effectiveness of these demonstration treatment programs, we developed a demographic profile of the persons entering the programs. When demographic data for the clients entering treatment between January and December 1986 (N=107) were compared with those for problem and pathological gamblers in the general population, some substantial differences were observed.

For example, only 7% (N=7) of the clients coming into the treatment programs were women, in contrast to 36% of the problem and probable pathological gamblers identified in our telephone survey ($\chi^2=18.14$, df=1, $p<0.01$). Only 9% (N=10) of the treatment program clients were nonwhite, compared with 43% of the problem and probable pathological gamblers identified in our survey ($\chi^2=10.05$, df=1, $p<0.01$). The percentage of problem and probable pathological gamblers under age 30 identified in our survey (38%) was much higher than the 18% (N=19) of program clients under age 30 ($\chi^2=5.86$, df=1, $p=0.01$). Our survey data on age were more consistent with the National Council on Compulsive Gambling finding that 33% of their callers seeking individual assistance in 1984–1985 were under age 30 than they were with the characteristics of gamblers in the state's treatment programs.

DISCUSSION

Pathological gamblers have been treated in a variety of settings, including self-help groups, private practice, VA and general hospital inpatient programs, and community mental health centers. Most research on pathological gambling is based on gamblers enrolled in inpatient treatment programs or recruited from Gamblers Anonymous (GA) (3–12). Several early studies were done with college undergraduates (13, 14) and patients in private practice (15). No comparisons have been made of pathological gamblers in treatment and problem gamblers in the general population. On the basis of the research that has been done, pathological gambling is widely believed to affect primarily upper-middle-class and middle-class white men in their 40s and 50s.

Pathological gamblers are believed to be highly employable and to have had fairly stable family lives until their gambling problems escalated. Problem gamblers identified in our New York survey did not fit such a profile. They were significantly younger than the patients entering treatment programs in the state. They were also far more likely to be women than were the patients in the three state-funded treatment programs. Problem gamblers in the New York population were more likely to be black or Hispanic, and they tended to have lower incomes and less education than the patients in treatment. Although these data raise a variety of interesting questions about the etiology and development of pathological gambling, they are most important in confirming that prevailing assumptions about the population of pathological gamblers have long been biased.

Preliminary analysis of prevalence surveys done in Ohio and Delaware (unpublished data of Culleton; unpublished data of Culleton and Lang) indicated that, as in New York, individuals classified as potential pathological gamblers and probable pathological gamblers were significantly different in terms of age, race, and sex from pathological gamblers in treatment (personal communication from Culleton). It is important to note that the ethnic disparities found in our New York data may not necessarily generalize directly to other parts of the United States. In areas of the country where Asians, Native Americans, or Central Americans are predominant minorities, these groups could be expected to be the ones underserved. We cannot determine from our data why identified pathological gamblers are younger than were previously thought. It is unclear whether there have been substantial changes in the population at risk, whether a biased profile from self-selected patients in treatment was developed, or whether young problem gamblers are able to control their wagering activities after a certain age. Ultimately, however, this question is less important than who needs services now.

If, as seems likely, problem gamblers in the general population differ substantially from pathological gamblers in treatment, it will be necessary to modify both the prevailing view of pathological gamblers and the types of outreach and treatment used with these individuals. It will be necessary to locate new treatment programs in minority communities, to consider new ways to pay for treatment in such programs, and to modify the treatment modalities used with problem gamblers. It will also be necessary to consider new forms of outreach to groups that might experience higher rates of pathological gambling than have been suspected.

Finally, it will be necessary to expand the scope of research done on pathological gambling to take the wider range of variation among pathological gamblers in the general population into account. This research will contribute to policy debates about ways to target public services to underserved groups of problem gamblers as well as to clinical debates about appropriate modes of treatment for minority, female, and youthful problem gamblers.

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A Follow-Up Investigation of Offspring of Parents With Bipolar Disorder

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Seven male children who each had a manic-depressive parent (five also had a parent with unipolar depression) and 12 control children were studied. The proband children had shown a range of adjustment problems as infants and toddlers. Four years later, they continued to have substantial behavior problems, including ones that could be classified as DSM-III *psychiatric diagnoses. On the basis of psychiatric interviews and psychological assessments, the proband children received more* DSM-III *diagnoses than the control children. Proband children reported internalizing symptoms; this pattern was corroborated by their mothers, who also characterized these children as showing antisocial behavior patterns.*

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Seven male infants, born over a short time span to families in a clinical research project in which one parent had been previously hospitalized for a bipolar disorder, were studied during their first 2 years of life. In five of the families, the parent with a bipolar disorder had a spouse with unipolar depression. The children showed substantial problems in early relationship formation and in social and emotional development (1–3). They were likely to have insecure attachment relationships with their caregivers and to have problems in regulation of affect. Problems in coping with stressful situations were common. Expressions of aggression were inappropriate, disproportionate, and displaced. The children found it difficult to share, and they showed deficits in role-taking and perspective-taking abilities.

This report provides data on the status of the same group of children when they were seen 4 years later to determine whether the problems identified early in their development reflected precursor patterns of later diagnosable disturbance. On the basis of previous research (4), it was predicted that children from this sample of severely ill parents would continue to show considerable problems.

METHOD

The seven male children who each had a manic-depressive parent were studied again at ages 5 and 6. Four of the parents with bipolar illness were female and three were male. Lithium had been prescribed for each of them. The parents' mean age at the onset of illness was 19.5 years (range=14–35 years), with an average of 4.4 years (range=2–12 years) of hospitalization. Diagnoses of bipolar affective disorder had been determined on the basis of interviews with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (5), according to the Research Diagnostic Criteria (6). Five of the seven spouses had been diagnosed as having unipolar depression, and one had substance abuse and war neurosis. The parents were high school and college educated (mean±SD years of education=15.9±3.0 for the mothers and 16.3±4.0 for the fathers).

A comparison group of 12 male children was used. The mean±SD number of years of education for control parents was 16.2±2.6 for the mothers and 18.3±2.2 for the fathers. The slight difference in the educational levels of the fathers in the two groups was not significant (t=1.42, df=17, n.s.). All children in both groups were the same ages at times of testing. The children in both groups were comparable with regard to number of siblings (the mean for each group was one sibling). Five (71%) of the seven proband children were firstborn, compared with seven (58%) of the 12 control children. One child in each group was black and the remainder were white. All of the mothers and seven of the fathers in the control group were diagnosis-free on the basis of SADS-L interviews. The remaining fathers were not given the SADS-L, but their Beck Depression Inventory scores were well within the normal range.

Informed consent was obtained after the procedures had been fully explained to the parents. Simple de-

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scriptions of the procedures were given to the children. Children's assent was not obtained because they were younger than the age required for assent (7 years), as determined by institutional policy.

At age 5 the children were observed in a laboratory setting in procedures chosen to assess the areas of difficulty that had been seen when they were 2 years old. They were observed in interaction with a playmate, sometimes under conditions of challenge and conflict, and they were given structured tests to assess empathy and conflict-resolution strategies. The empathy tests were designed to determine the extent to which children can make appropriate inferences about the emotions of others, particularly emotions of pleasure and distress. The test of conflict resolution provides information about children's strategies for coping with hostility and aggression.

At age 6 the children returned for psychiatric and psychological evaluation. A standard psychiatric interview, the Child Assessment Schedule (7), was given. This interview consists of questions concerning problems in each of the following areas: school, friends, activities, family, self-image, fears, worries, moods (depression), physical complaints, and acting out (see reference 7 for a discussion of the reliability and validity of the instrument). The mothers filled out the Achenbach Child Behavior Checklist (8). Areas identified by the Achenbach checklist for this age group include both internalizing problems (depression, withdrawal, physical complaints, schizoid behavior, obsessive-compulsive behavior) and externalizing problems (hyperactivity, aggression, delinquent tendencies) (see reference 8 for a discussion of the reliability and validity of this instrument). *DSM-III* diagnoses were determined by a psychiatrist (D.H.M.) in collaboration with a psychologist who administered the Child Assessment Schedule to each child. Diagnoses were derived mainly from the child's responses to the psychiatric interview and data obtained from the Achenbach checklist filled out by the mother. Areas of concern (emotional problems that did not meet diagnostic criteria) also were identified in the psychiatric evaluation. The psychiatrist, the psychologist, and other testers did not know the diagnoses of the parents.

RESULTS

The psychiatric diagnoses and areas of concern identified in the children are presented in table 1. The percentages of children in the proband and control groups who showed each type of problem are indicated. The diagnoses and symptoms of the proband children reflected considerable variety and severity of disturbance. For example, several of the proband children, but none of the control children, received diagnoses of overanxious disorder, depression, and/or conduct disorder. The proportion of children in the proband group who showed two or more psychiatric diagnoses or areas of concern was significantly greater than that in the control group ($\chi^2=6.05$, df=1, $p<0.025$, with Yates' correction for continuity). Despite directional predictions, two-tailed tests of significance were used throughout in order to impose stringent conditions for rejection of null hypotheses. Only one child in the proband group did not receive a formal diagnosis at the time of data collection. Shortly thereafter he was identified by school authorities as experiencing depression and separation problems and was referred for therapy. (Three other children in the proband sample were in therapy as well.) When severity of disturbance was operationalized to include having multiple diagnoses and/or receiving treatment for emotional problems, the difference in the proportions of children in the proband and control groups (100% versus 8%) was highly significant ($\chi^2=11.71$, df=1, $p<0.001$).

TABLE 1. Psychiatric Problems in Children of Parents With Bipolar Disorder and in Control Children

	Proband Group (N=7)		Control Group (N=12)	
Problem	N	%	N	%
DSM-III diagnosis				
Depression	3	43	0	0
Conduct disorder	3	43	0	0
Overanxious disorder	3	43	0	0
Obsessive-compulsive disorder	1	14	0	0
Separation anxiety disorder	3	43	3	25
Simple phobia	0	0	2	17
Developmental language disorder	1	14	0	0
Area of concern				
Self-destructive behavior	1	14	0	0
Dysthymia	1	14	1	8
Anger	2	28	0	0
Anxiety	0	0	3	25
Attentional problems/impulsivity	2	28	0	0
Two or more problems in same child	6	86	1	8

Although there was considerable diversity in the types of problems shown by proband children, there were also some common themes. Proband children were likely to show both internalizing and externalizing problems. This issue was explored in greater detail in the next two sets of analyses.

Standardized scores (8) on the Achenbach checklist, summed across subscales separately for internalizing and externalizing symptoms, were compared for the two groups of children. Proband children scored higher than control children on internalizing problems (probands' mean±SD score=62.1±10.1; control children's score=49.5±8.0; F=9.10, df=1, 17, $p<0.01$) and on externalizing problems (probands, 62.4±9.3; control children, 50.5±6.5; F=10.99, df=1, 17, $p<0.005$). (The Bonferroni correction for inflated type I errors due to multiple tests yielded an operating p value of 0.025 for the 0.05 significance level we adopted.) Descriptive analyses (i.e., visual inspection of means) indicated that the categories which contributed most to the overall group differences on internalizing problems were withdrawal and obsessive-compulsive behavior. For externalizing problems, the proband children scored higher than the control children on each of the three subscales: hyperactive, aggressive, and delinquent.

Categories of problem areas on the Child Assessment Schedule were organized to produce 1) an internalizing dimension (the summed scores for fears, worries, moods, and physical complaints were combined), 2) an externalizing dimension (the summed score for acting-out behavior was used), and 3) an adjustment dimension (the summed scores on problems with school, friends, family, and activities were combined). The self-image problem area was not included in any of the conceptual groupings used in the final statistical analyses. Exploratory analyses indicated very different (and counterintuitive) patterns, with the children of bipolar depressed parents reporting *fewer* self-image problems than control children (mean±SD for probands=1.9±0.9; for control children, 2.8±0.8; $F=5.67$, $df=1, 17$, $p<0.05$). Children from the proband and control groups differed on the internalizing dimension (mean±SD score for the probands= 30.9±12.0; for the control children, 19.6±6.6; $F=7.09$, $df=1, 17$, $p=0.016$). Visual inspection of means indicated that the groups differed most on fears, followed by moods (depression), and worries, with few differences on physical complaints. The groups did not differ on the externalizing subscale (mean±SD score for the probands=10.4±4.0; for control children, 8.7±2.5; $F=1.43$, $df=1, 17$, n.s.). There were no differences on adjustment problems (mean±SD score for the probands=14.±7.0; for control children, 12.9±4.1; $F<1$). (In this case the Bonferroni correction produced an operating p value of 0.017 for the 0.05 significance level we adopted.)

Children in the proband group tended to show less insight than control children on two different empathy tasks (mean±SD score for the probands=3.57±1.40; for control children, 4.83±1.40; $F=3.59$, $df=1, 16$, $p<0.10$; and probands, 5.00±1.41; control children, 6.25±1.54; $F=3.07$, $df=1, 16$, $p<0.10$). In contrast, in conflict situations, the proband children generated more problem-solving strategies—particularly, nonaggressive strategies such as sharing or acquiescence as a means of resolving conflict—than did the control children (mean±SD for the probands=2.57±1.14; for control children, 1.09±1.58; $F=4.60$, $df=1, 16$, $p<0.05$). Their special sensitivity to conflict also was evident in laboratory assessments: more proband children reported distress than did control children (86%, N=6, versus 17%, N=2) after having observed a simulated argument between two female adults ($\chi^2=6.05$, $df=1$, $p<0.025$).

DISCUSSION

Patterns of maladjustment that had been identified in a small group of toddler-age children who each had a parent with a bipolar disorder were evident again 4 years later. Difficulties in empathy or role taking and unusual patterns of conflict resolution were common themes in both periods of development. Psychiatric problems, particularly depressive symptoms and antisocial orientations, were also prominent at age 6. Early disturbances in the self-system, relationship formation, and regulation of affect thus may serve as markers for later problem behaviors. Some of the problems identified in the children (e.g., the attenuated insight and empathy and the atypical patterns of dealing with conflict) also parallel patterns commonly identified in adult bipolar patients, which patterns in turn have been viewed as psychodynamic processes linked with familial transmission of disturbances in regulation of affect (9, 10). Bipolar patients are often described as having difficulty dealing with anger and conflict, and it should not be surprising to see this theme echoed in family and parent-child interactions. Explosive encounters were commonly articulated in the families we studied. The data suggest that children deal with conflict by developing at an early age strategies that involve "keeping the peace," i.e., sharing and submissiveness.

The small sample size precluded statistical analyses of longitudinal patterns of continuity and discontinuity in problem behaviors over time. However, our clinical impressions are detailed here. The four proband children who had the most problems at follow-up had also been identified 4 years earlier, by different (but not blind) observers, as having more severe problems than the remaining three children. There was variability across children in types of problems shown over time. Some children showed marked stability. Other children showed different symptoms at the two time periods.

Several other studies have reported problems in the offspring of parents with bipolar disorder, but some of these children have been described as "supercompetent" (4, 11). The present research is the first, to our knowledge, to indicate how early the problems emerge, but it provides few additional insights regarding mechanisms of transmission. Because of the small sample size, the presence of psychopathology in both parents, and the nature of the research design, it is not possible to discern causal mechanisms. Family histories of affective disorder were present for all of the parents with bipolar disorder and for five of their spouses, but patterns of environmental disturbance were also evident both when the proband children were seen as toddlers and at follow-up. At follow-up, separations or divorces had occurred (or were under active consideration) in five of the seven families. Exploration of stressful life events (by A.M.) indicated disorganization, bizarre events, unpredictability, and alienation in most of these families.

Research is needed to identify genetic and experiential contributors to children's outcomes, that is, to examine, within samples of parents with bipolar illness as well as in comparison groups, the specific conditions that determine more favorable versus less favorable outcomes for offspring. The present findings indicate that, for families like those represented in this study, it will be important to monitor closely the link between parent-child interaction and outcome for the child and to consider therapeutic intervention early in the child's development.

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Ostensible Agency: Another Malpractice Hazard

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Under the tort doctrine of ostensible (apparent) agency, a psychiatrist was named as a codefendant in a psychiatric malpractice suit against a nonmedical psychotherapist employed in his medical group, who had treated the plaintiff in her private practice in the same offices. The psychiatrist was later dismissed as a defendant, but to avoid being sued in such a case, a psychiatrist contemplating an association with another professional should 1) check the professional's record with the appropriate licensing agency, 2) require proof of licensure and malpractice insurance, 3) require that the professional's private patients sign disclosure statements, and 4) assure that names on written materials are kept separate.

(Am J Psychiatry 1988; 145:510–512)

The most frequent bases for medical malpractice claims against psychiatrists and the relevant underlying principles of tort law have been discussed in several excellent review articles (1–5). However, I have been unable to find a single case report involving an allegation of liability on the part of a psychiatrist based on the acts of a nonmedical psychotherapist who was not acting as an employee or supervisee of the psychiatrist. In this article I will present such a case. To protect the confidentiality of all parties to the lawsuit discussed here, I will use pseudonyms for both the individuals and the business entity.

CASE REPORT

John Jones, M.D., a psychiatrist, established a medical group, Forensic Psychiatry Associates, under California law. At that time, he hired as employees two licensed marriage and family counselors: Thelma Rose, M.A., and Virginia Rader, M.A.

Under the employment agreement, Mses. Rose and Rader were to be employed by Dr. Jones and by Forensic Psychiatry Associates. It was also mutually agreed that each of the three parties could see his or her own private patients, outside the scope of the employment relationship, in the same suite of offices. The office suite had a single door. The nameplate on the door read as follows:

Forensic Psychiatry Associates
A Medical Group

John Jones, M.D.
Thelma Rose, M.F.C.C.
Virginia Rader, M.F.C.C.

Several years after Forensic Psychiatry Associates was established, Bonnie Lewis, a private patient of Ms. Rose, sued Ms. Rose, Ms. Rader (who had referred her to Ms. Rose), and 10 "Doe" defendants for malpractice, allegedly committed during the time the employment agreement was in force. By the time of the lawsuit, Mses. Rose and Rader had left Dr. Jones's employ.

The stated causes of action for the alleged malpractice were multiple and complex and are not relevant to the purposes of this article.

A year after the suit was brought, Dr. Jones was substituted in as one of the "Doe" defendants on the basis of Ms. Lewis's stated belief that Dr. Jones had supervised Ms. Rose's treatment of her. During the discovery stage of the lawsuit, it was quickly established that Dr. Jones had no knowledge whatsoever of Ms. Lewis and had first learned of the lawsuit when he was served with the summons and complaint.

In his individual capacity and as president of Forensic Psychiatry Associates, Dr. Jones had a malpractice insurance policy that had been in force during the period in question. The professional activities of Ms. Rose and Ms. Rader were also covered under that policy but only to the extent of their practice within Forensic Psychiatry Associates and not for any private practice activities. Neither Ms. Rose nor Ms. Rader had individual malpractice insurance coverage, and it was clear (from the fact that Dr. Jones was not one of the original named defendants and was only substituted in as a defendant 1 year after the case was filed) that Ms. Lewis's attorney had discovered that neither Ms. Rose nor Ms. Rader had malpractice coverage and was therefore looking for a "deep pocket." It was further revealed that Ms. Rose had submitted fee statements to Ms. Lewis on her own letterhead and that Ms. Lewis had made out her checks directly to Ms. Rose, who endorsed and deposited them. The name of Dr. Jones or of Forensic Psychiatry Associates was not associated with any of these transactions.

Dr. Jones's attorney attempted to obtain a summary

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judgment in Dr. Jones's favor on the basis of the facts just outlined. However, Ms. Lewis had alleged in her deposition that she had believed Dr. Jones was supervising her treatment; this belief was reportedly based mainly on the manner in which the corporate entity and the individuals were listed on the office door. Since only "a scintilla" of contrary evidence is necessary to defeat a motion for summary judgment, this motion was denied and Dr. Jones continued as a codefendant for 3 more years, while further discovery was conducted in the case.

In the course of these proceedings Ms. Rose and Ms. Rader requested legal representation under Dr. Jones's and Forensic Psychiatry Associates' malpractice insurance policy. The carrier did, in fact, provide this representation, since the question of whether or not Ms. Rose's treatment of Ms. Lewis was within the scope of her duties under the employment contract was one of the issues in the litigation and since the carrier was concerned that it might be open to an allegation of bad faith (and, hence, punitive damages) if the representation that was requested by Ms. Rose and Ms. Rader were declined.

The case was concluded by settlement before the trial. In the settlement Dr. Jones and Ms. Rader were dismissed as defendants, with prejudice (i.e., with Ms. Lewis's being barred from reopening any litigation against them on the same grounds). The carrier paid $75,000 to Ms. Lewis on behalf of Ms. Rose only and with no admission of her liability. Dr. Jones did not want to consent to payment being made under his policy (even though this payment was made on behalf of Ms. Rose only) but was told by the attorneys for the insurance carrier that he had standing to withhold his consent to settlement only as it regarded himself and did not have such standing vis-à-vis the codefendants.

DISCUSSION

The concept of vicarious liability in tort law is well established. It is based on the concept of agency or *respondeat superior*, i.e., a person (or corporate entity) is held to be liable for the damages flowing from the negligent actions of an employee (servant) if the alleged negligence was within the scope of the employee's duties (6). By extension, the employer might also be liable for the negligent actions of an employee, even when these actions are not within the scope of the employee's duties, if the plaintiff reasonably believed that the actions in question were directed by the employer (7). This is the concept of ostensible (or apparent) agency.

In the case reported herein, the objectively tenuous connection between Dr. Jones and Ms. Lewis represented by the nameplate on the office door was enough to defeat Dr. Jones's motion for summary judgment and to have the issue brought before a jury (had the case been continued to trial). The issue of whether Dr. Jones might ultimately have been found to be negligent (and, hence, liable under the principle of ostensible or apparent agency) is speculative, since this case did not proceed to trial. However, the possibility remains that the jury might have found Ms. Lewis credible (and, hence, Dr. Jones liable). The institutional structure of mental health care in the United States places the psychiatrist uniquely at risk for this type of medical malpractice claim.

In California and many other states, psychotherapy may be provided by psychiatrists (and legally—although not commonly—by other licensed physicians) and by licensed psychologists (with Ph.D.s), licensed clinical social workers, licensed marriage or family counselors, and mental health nurse practitioners. These nonmedical psychotherapists may practice independently and also in formal relationships with each other and with psychiatrists. Further, psychiatrists are the only physicians who in some cases share offices with nonmedical psychotherapists, sometimes even without a formal employer-employee or partner relationship.

When the nonmedical psychotherapist is, in fact, acting under the supervision and direction of the psychiatrist, the potential liability of the psychiatrist for the malpractice of the nonmedical therapist is clear under the usual tort concept of agency. However, when the nonmedical psychotherapist is practicing independently of the psychiatrist but is physically within the same office, the psychiatrist might still be joined as a defendant in any malpractice action brought against the nonmedical therapist, on the basis of the principle of ostensible agency. In fact, the very multiplicity of types of relationships between a psychiatrist and a nonmedical psychotherapist lends credibility and reasonableness to the plaintiff's avowed belief in the existence of a superior-agent (master-servant) relationship.

On the basis of my experience in medical malpractice consultation and conversations with other psychiatrists and attorneys, I have formulated a list of simple "self-defense" measures that would greatly minimize the risk of such malpractice exposure.

First and simplest, any psychiatrist who is contemplating sharing an office with a nonmedical psychotherapist should first check with the appropriate licensing agency and/or professional organization to make sure that no complaints, formal charges, or licensure sanctions are on record against that psychotherapist.

Second, the psychiatrist should require documentation of current valid licensure and malpractice insurance coverage for the nonmedical therapist, as well as proof of renewal of such licensure and insurance coverage at appropriate intervals.

Third, the psychiatrist should require each of the nonmedical therapist's private patients to sign a disclosure form similar to that shown in appendix 1. The original of this form should be retained by the psychiatrist, and copies should be given to the nonmedical therapist and to his or her patient.

Fourth, the names on such written materials as office nameplates, professional cards, letterheads, and billing forms should be kept separate.

These measures are also recommended for a psychiatrist contemplating an association with another psychiatrist, either a formal partnership or employment or merely the sharing of an office.

Under the American legal system, of course, no private citizen has an absolute immunity to lawsuits. However, the simple and easily implemented precautions listed here at least can reduce the likelihood of an "innocent" psychiatrist's being named as a defendant in a lawsuit based on ostensible or apparent agency.

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APPENDIX 1. Sample of Statement Signed by Private Practice Psychotherapy Patient Seen in Offices of Group Practice

DISCLOSURE STATEMENT

I understand that Forensic Psychiatry Associates is allowing my psychotherapist, [name of therapist], to use its facilities for his/her private patients, on a space-available basis.

This confirms my understanding that my treatment by [name of therapist] has no connection with John Jones, M.D., or with Forensic Psychiatry Associates.

________________ Date

________________ Name of Patient

________________ Signature of Patient

________________ Signature of Therapist

Meige's Syndrome Associated With Neuroleptic Treatment

Jambur Ananth, M.D., Evelyn Edelmuth, M.D., and Balbinder Dargan, M.D.

Meige's syndrome is characterized by blepharospasm and oromandibular dystonia. Three cases are presented; two were associated with long-term neuroleptic administration. This drug-induced syndrome may be a variant of tardive dystonia, and prompt discontinuation of neuroleptic treatment may be therapeutic.

(Am J Psychiatry 1988; 145:513–515)

In 1910 Meige (1) described a syndrome of idiopathic blepharospasm and oromandibular dystonia. This syndrome occurs more often in females than in males (2:1) and most often between the ages of 30 and 70 years (2, 3). Its characteristic features include bilateral blepharospasm and involuntary movements of the lower face, neck, and jaw (2, 3). Rarely, muscles of other areas are affected. The typical feature of this disorder is the involvement of the orbicularis oculi muscle. During the initial stages an increased rate of blinking is noted, and later in the course of the disease uncontrollable eyelid spasms occur (4). The spasms can assume a tonic form (blepharotonus) and involve rhythmic contractions that obstruct vision. This blepharospasm may last from several seconds to many minutes and can be triggered by an attempt to look upward or by stress. Since blepharospasm disappears during sleep and is under partial voluntary control, a peripheral neuromuscular lesion is unlikely. A sudden voluntary effort or a voluntary facial movement often leads to opening of the eyelids for variable periods of time. Extended rest or darkness can improve the condition temporarily. Since blepharospasm disrupts vision and activities that depend on vision, such as driving a motor vehicle, the condition causes considerable disability.

We now report three cases of Meige's syndrome: one of spontaneous origin and two associated with neuroleptic drug treatment.

CASE REPORTS

Case 1 (idiopathic). Ms. A, a 45-year-old married white mother of two children, worked as a professional and had always enjoyed good physical and mental health. Shortly after an uneventful abdominal operation involving general anesthesia several years ago, she noticed blepharospasm. A month after the surgery, she noticed increased eye blinking, for which no action was taken. Gradually, she developed more intense contraction of her eye muscles, which was frequently precipitated by emotional stress and at times obstructed her vision. Extensive neurological and psychiatric evaluations did not reveal any positive findings. In fact, Ms. A did not have any psychiatric symptoms at all. Various medications, including diazepam, imipramine, amantadine, pyridoxine, and haloperidol, did not produce any appreciable change. Although there was some benefit from the anticholinergic antiparkinsonian agent trihexyphenidyl, Ms. A continued to live with the same distressing symptoms.

Case 2 (associated with haloperidol). Ms. B, a 40-year-old single unemployed white woman, lived alone near her parents and had worked as a secretary for 7 years before leaving her job. Except for her mother's mild late-onset diabetes, she had no family history of any major illness, including neurological and psychiatric disorders. As a result of learning difficulties, psychiatric treatment was sought for Ms. B when she was 10. She was reported then to be intelligent but impulsive, anxious, and unduly attached to her parents; until the time of her marriage at age 20, she slept with her parents. Six months after the marriage, Ms. B was divorced from her husband and sought psychiatric help because of her inability to live alone, severe anxiety, and multiple phobias. At that time she showed no evidence of any neurological disorder, specifically blepharospasm or blinking. At age 24, however, she was hospitalized briefly because of these symptoms and

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TABLE 1. Comparison of Spontaneous and Neuroleptic-Induced Meige's Syndrome With Other Neuroleptic-Related Disorders

Variable	Neuroleptic-Induced Dystonia	Tardive Dyskinesia	Meige's Syndrome: Spontaneous	Meige's Syndrome: Neuroleptic-Induced
Typical age	10–50 years	Risk rises with age	30–70 years	Not known
Sex	More males	Both	More females	Both
Presenting symptoms	Acute spasm of voluntary muscles	Usually none	Inability to see	Inability to see
Sites of occurrence	Eyes, tongue, throat, neck, chest, extremities	Face, tongue, trunk, extremities	Eyelids, face	Eyelids, face
Exposure to neuroleptics	Present	Present	Usually absent	Present
Family history	None	None	Extrapyramidal disease	None
Course	Transitory, recurrent	Chronic, slowly remitting	Chronic	Temporary
Prognosis	Good	Variable	Variable	Fair
Disability	Temporary	Variable, usually mild	Severe	Severe
Response to anticholinergics	Good	Minimal	Minimal	Minimal
Emotions	Exacerbated	Exacerbated	Exacerbated	Exacerbated
Status during sleep	Disappears	Disappears	Disappears	Disappears

had inadequate responses to diazepam, chlordiazepoxide, lorazepam, imipramine, clomipramine, desipramine, trimipramine, and phenelzine. Ms. B thereafter frequented emergency rooms and consulted many doctors, without relief of her distressing anxiety symptoms. When she was 28, haloperidol was prescribed at a dose of 1 mg/day. She responded well, so the same treatment was continued at 1–4 mg/day for the next decade.

At age 39 Ms. B started to complain of frequent blinking, which was exaggerated by stress and anxiety. Ophthalmologic examination did not reveal any pathology. Gradually, over several months, she complained that her eyes frequently closed involuntarily and were difficult to open, especially in stressful situations such as a job interview or driving in traffic. Hence, she stopped driving and working and returned to live with her parents. The possibility of spontaneous Meige's syndrome or tardive dyskinesia was considered, but there were no oral, lingual, or systemic choreoathetotic movements typical of tardive dyskinesia. Antiparkinsonian agents, benzodiazepines, and propranolol failed to relieve the isolated symptoms of blepharospasm. Haloperidol treatment (3 mg/day) was gradually discontinued. Six months later the blepharospasm was greatly relieved, although a mildly increased frequency of blinking continued. Ms. B was still anxious and unemployed but was living independently.

Case 3 (associated with thioridazine). Mr. C, a 29-year-old single white man, came to the emergency room because of 2 weeks of excessive blinking and bilateral involuntary contractions of his eyelids associated with spasms of his facial muscles. The condition had not responded to treatment with benztropine mesylate, 4 mg/day for 2 weeks. During the episodes of blepharospasm, Mr. C had difficulty keeping his eyes open. At the time of his emergency room visit, he was found to have bilateral blepharospasm, which lasted for several minutes and was worsened by looking upward and by anxiety. He had taken thioridazine more or less steadily for the past 6 years (50–300 mg/day, 50 mg/day in the last 2 years) because of three episodes of psychosis with auditory hallucinations. Because there was no evidence of any previous neurological disorder or blepharospasm, a drug-induced tardive dyskinesia was suspected. Mr. C had discontinued the drug for 7 days before coming to the emergency room, and this had worsened the blepharospasm. A diagnosis of neuroleptic-associated Meige's syndrome was entertained on the basis of the clinical picture, drug history, and an unremarkable family history for psychiatric or neurological illness. The frequency and intensity of blepharospasm decreased after restitution of the same low dose of thioridazine.

DISCUSSION

The case histories of the three patients presented in this report describe the typical clinical features of Meige's syndrome; in two cases the symptoms were drug induced, and in the other they were idiopathic. The clinical pictures of all three cases were indistinguishable.

The possibility that Meige's syndrome can be induced by long-term neuroleptic treatment suggests that a similar pathophysiology may play a role in both the drug-induced and spontaneous forms of this syndrome. Dopaminergic supersensitivity may contribute to this pathophysiology.

Because it is not widely known that Meige's syndrome can result from long-term neuroleptic therapy, such cases may go unrecognized or be confused with tardive dyskinesia. It is important to differentiate this condition from other disorders with similar symptoms (see table 1). While idiopathic Meige's syndrome affects patients between ages 30 and 70 (5), the drug-induced syndrome occurs in younger patients (6). In addition, the lack of prompt response to anticholinergic drugs in cases of idiopathic Meige's syndrome is important in differentiating it from acute dystonia, which does respond to anticholinergics (7). Patients with the idiopathic syndrome may also have family histories of essential tremor, Parkinson's disease, abnormal facial movements, blepharospasm, and concomitant physical illnesses, such as autoimmune disorder, parkinsonism, and multiple sclerosis. Many of these patients may manifest obsessive-compulsive disorder and depression (5). Tardive dystonia, occurring in chronic psychotic patients, can be differentiated by a history of long-term neuroleptic use and the presence of both dyskinetic and dystonic movements. Prompt diagnosis is important since the neuroleptic-associated

Meige's syndrome can obstruct vision, especially under stressful conditions such as driving, with dangerous consequences, and if it is recognized early, withdrawal of the offending neuroleptic may lead to recovery.

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Alternative Patterns of Seasonal Affective Disorder: Three Case Reports From North India

Rajeev Gupta, M.D.

Three cases of seasonal affective disorder in north India are described, illustrating different seasonal patterns: 1) mania in summer and depression in winter, 2) mania in early winter and depression in late winter, and 3) depression in summer and mania in early winter.

(Am J Psychiatry 1988; 145:515–516)

Seasonal affective disorder is characterized by recurring cycles of fall-winter depression and spring-summer euthymia, hypomania, or mania. The depressive symptoms often include hypersomnia, anergia, fatigue, carbohydrate craving, and weight gain. The syndrome occurs predominantly in women and begins in early adulthood (1). Recently Bick (2) described cases of severe seasonal major affective disorder with hypomania during summer and depression in winter. In another report Rosenthal et al. (3) described seasonal affective disorder in children and adolescents with a similar seasonal pattern.

To my knowledge, no other pattern of seasonal affective disorder has been reported. During my clinical practice in the Punjab, in north India, I have observed the following three patterns of seasonal affective disorders: 1) hypomania or mania during the summer and depression in winter, 2) hypomania or mania in early winter and depression in middle and late winter, and 3) severe depression in summer and hypomania or mania in winter.

CASE REPORTS

Case 1. Ms. A, a 53-year-old woman, fulfilled the *DSM-III* criteria for bipolar illness. When she was 44, during June she developed florid mania and was hospitalized. She was treated with pharmacotherapy and ECT. In the next 5 years, during June and July she developed manic excitement, each time characterized by increased psychomotor activity, inappropriate euphoria, an increase in physical energy, insomnia, and a tendency to overspend. She developed severe depression each November and December. Her depressive episodes were characterized by withdrawal, psychomotor retardation, insomnia, suicidal ideas, and loss of appetite. The depression always continued until April or early May. Twice during depressive episodes she made suicide attempts. Three times she was hospitalized for treatment of manic excitement, always in the summer. She had no family history of affective disorder. Her depressive episodes did not respond well to drug treatment. Twice she received ECT during depressive

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episodes. She eagerly awaited the spring, when she invariably began to feel better. For the 2 years before I saw her, she was receiving prophylactic lithium treatment (900 mg/day). Her serum lithium level was maintained at 0.6–1.0 meq/liter. She did not respond to lithium prophylaxis.

Case 2. Ms. B, a 46-year-old woman, had received lithium prophylaxis for the past 2 years. For the past 6 years she had experienced attacks of manic excitement in early winter. During October and November she talked more; became euphoric, grandiose, and energetic; displayed unprovoked anger; and at times turned violent. From December to early March she remained severely depressed. Her depressive episodes were characterized by sadness, weeping spells, loss of interest in work and household activities, insomnia, anorexia, and feelings of helplessness. She was diagnosed as suffering from bipolar affective disorder according to *DSM-III*.

Three times Ms. B was hospitalized and received ECT, twice for mania and once for depression. She remained completely asymptomatic from April to September. There was no history of affective disorder in her first-degree relatives.

Although lithium prophylaxis was twice prescribed for Ms. B, she discontinued it during illness-free periods.

Case 3. Ms. C, a 70-year-old woman, was brought to the clinic in November with complaints of increased activity, elation, ideas of grandiosity, and unprovoked anger of 3 weeks' duration. A mental status examination revealed irritability, pressured speech, and grandiosity. She had experienced similar attacks of excitement during October, November, and December each year for the past 15 years. During June and July she became slow, retarded, anorexic, and sad and cried without reason. She remained in her room. Three times she was admitted to a mental hospital for treatment of manic excitement, for which she received ECT. For another four manic episodes she received ECT as an outpatient. Her depressive attacks had a tendency to improve without any psychiatric treatment. Four times she was treated with lithium prophylaxis, but she stopped taking lithium during illness-free periods. She fulfilled the *DSM-III* criteria for bipolar affective disorder. Her oldest son, a paternal uncle, and two maternal aunts had bipolar affective disorder.

DISCUSSION

Situated in northwest India, the Punjab Plains (27°39′ to 32°30′ north latitude and 73°51′ to 77°36′ east longitude) constitute a significant part of the Great Plains of India. The elevation of the Punjab Plains is 693–1,007 feet above sea level. The climate of the Punjab is characterized by dryness except in the brief monsoon period, a very hot summer, and a bracing winter. The cold season is from the middle of November to early March. The succeeding period, up to about the end of June, is the hot season. July, August, and the first half of September constitute the monsoon. The temperature increases rapidly after February. June is generally the hottest month; the mean daily maximum temperature is 105°F, and the mean daily minimum temperature is 81°F. The summer days are 12½–13½ hours long. With the onset of the monsoon in July, there is an appreciable drop in the daytime temperature, but the nighttime temperatures during the monsoon are nearly as high as in the later part of the summer. After about mid-September, when the southwest monsoon withdraws, the nighttime temperature decreases rapidly, but the drop in the daytime temperature is not so rapid. From about November, however, both the daytime and nighttime temperatures decrease rapidly until January, which is the coldest month. The mean daily maximum temperature in January is 67°F, and the mean daily minimum is 44°F. Often during the winter season cold waves cause the minimum temperature to drop to below the freezing point. In winter, the days are nearly 10–11 hours long.

In the Punjab, mental health professionals often observe that a large number of patients with manic-depressive psychosis and their families recognize the effect of the change of season on relapse and change in polarity of the illness. The exact prevalence of this phenomenon has not been studied so far. It is estimated that roughly 10%–15% of the patients with severe affective illness have seasonal affective disorder. In the months preceding a change of season, patients are frequently brought to psychiatric services for prophylactic treatment of impending attacks of mania or depression. In some cases, peaks of affective episodes have coincided with peaks of the seasons.

Is it possible that there are different types of seasonal affective disorders in different parts of the globe? Earlier reports have come from the West. The incidence and prevalence of seasonal affective disorder have not been widely reported from different parts of the world.

Earlier reports on seasonal affective disorder described only a tendency toward spring and fall peaks of depression and summer peaks of hypomania or mania. I have described two variations of seasonal affective disorder, indicating that there may be more patterns of seasonal affective disorder than have been described in the literature.

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A Prospective Survey of Neuroleptic Malignant Syndrome in a Short-Term Psychiatric Hospital

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Of 1,470 patients treated with neuroleptics during 1 year at a private psychiatric hospital, only one patient developed neuroleptic malignant syndrome—an annual frequency of 0.07%. Use of low doses of neuroleptics may account for this frequency, which is below recent estimates.

(Am J Psychiatry 1988; 145:517–518)

Neuroleptic malignant syndrome, a presumed toxic reaction to antipsychotic drugs, is characterized by hyperthermia, muscular rigidity, altered consciousness, and other disturbances of hypothalamic and neuromuscular function (1). Since Caroff's 1980 review of neuroleptic malignant syndrome (2), scientific references to the disorder have mushroomed, clinical awareness of it has grown pari passu, and estimates of its prevalence have suggested that although it is not common, neuroleptic malignant syndrome is not rare.

Guze and Baxter (3) estimated that neuroleptic malignant syndrome occurs in 0.5%–1.0% of patients exposed to neuroleptics, and retrospective surveys have placed the annual rate between 0.4% and 1.4% (4, 5). Keck et al. (6) found a 0.9% frequency in their 18-month prospective survey. We report here on a prospective survey of neuroleptic malignant syndrome during 1 year in a short-term psychiatric hospital.

METHOD

This survey took place at a 118-bed private psychiatric hospital between June 1986 and June 1987. During that time, the hospital admitted 2,173 patients, who stayed for a median of 13 days (25th percentile=6.5 days; 75th percentile=22 days). Fifty-three percent (N=1,152) of the patients were female, and 47% (N=1,021) were male. Their median age was 32 years (range=15–83 years). Affective disorders were diagnosed in 70% and schizophrenia, schizoaffective disorders, and character disorders in another 20% of the patients.

We initially educated medical and nursing staff members about neuroleptic malignant syndrome by means of reading assignments and seminars. Throughout the year one of us made rounds daily; we were also available for consultation. We made our diagnosis of neuroleptic malignant syndrome using the criteria of Pope et al. (4).

RESULTS

During the year of the survey, approximately 1,470 patients at the hospital took neuroleptic medications. Table 1 lists the five most commonly prescribed drugs. Only one patient developed neuroleptic malignant syndrome.

Case Report

Mr. A, a 28-year-old man with bipolar affective disorder and a history of drug abuse, had been hospitalized for the first time at a state facility and treated with chlorpromazine, up to 1600 mg/day. After 36 hours he had developed fever, rigidity, and a creatine phosphokinase level of 470 IU/liter (normal=0–235 IU/liter). His physicians made a diagnosis of lobar pneumonia, but given the possibility of neuroleptic malignant syndrome, they discontinued the chlorpromazine and substituted clonazepam, 12 mg/day.

Two weeks later, Mr. A was transferred to our hospital and treated with haloperidol, up to 50 mg/day. After a month he had improved and was discharged on a regimen of haloperidol, 20 mg/day, amitriptyline, 125 mg/day, and lorazepam, 0.5 mg t.i.d.

About 10 days later, Mr. A was readmitted to our hospital with a paranoid psychosis. In addition, he showed parkinsonian symptoms and complained of difficulty swallowing. Results of a physical examination were normal except for a pulse of 120 beats/minute and a creatine phosphokinase level of 1400 IU/liter. Neuroleptics were withheld. Treatment with benztropine, chlordiazepoxide, and diphenhydramine was not helpful, and over the next 2 days Mr. A's blood pressure ranged from 160/120 to 140/100 mm Hg, his pulse varied from 104 to 128 beats/minute, and his rectal temper-

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TABLE 1. The Most Commonly Prescribed Neuroleptics at a Private Psychiatric Hospital During 1 Year

Drug	Percentage of Total Drugs Prescribed[a]	Median Dose (mg/day)	Dose Range (mg/day)
Haloperidol	22	10	2–40
Perphenazine	21	22	12–52
Thioridazine	14	150	50–350
Trifluoperazine	13	11	2–40
Chlorpromazine	11	125	15–550

[a]These five drugs represent 81% of the neuroleptics prescribed during the year.

ature rose to 101.8°F. He became progressively less responsive, was diaphoretic, and stopped taking food and fluids. Transferred to a medical facility, he subsequently developed aspiration pneumonia but ultimately improved on a regimen of antibiotics, dantrolene, bromocriptine, and lorazepam. He was transferred to a state hospital for further care.

Over the course of the year, four other patients with histories of neuroleptic malignant syndrome were admitted to the hospital. Three were treated with nonneuroleptic therapies. One was rechallenged with haloperidol in low doses and did not develop any evidence of reemergent neuroleptic malignant syndrome.

We also had six suspected cases of neuroleptic malignant syndrome that were ultimately diagnosed as other conditions. One was a catatonic reaction in a patient with bipolar illness. Two other patients had severe extrapyramidal reactions to neuroleptic drugs but no other evidence of neuroleptic malignant syndrome. Three patients had extrapyramidal reactions plus fever, which was attributed to coincident infections.

DISCUSSION

During the course of 1 year, we saw only one case of neuroleptic malignant syndrome in our short-term psychiatric hospital—a frequency of 0.07% (95% confidence interval=0.007%–0.4%), which is lower than recent retrospective estimates, although the upper end of our confidence interval is comparable. How can we account for this?

Since the median length of stay at the hospital was 13 days, we have only a "snapshot" of patients' courses of antipsychotic drug therapy. Thus, our 1-year prevalence figure represents 1 year in the life of an institution, not the rate for patients exposed to neuroleptics during that year. Nevertheless, many patients had been previously exposed to antipsychotic agents, and the highest risk of developing neuroleptic malignant syndrome seems to occur early in the course of treatment, when doses are being increased (5).

Could our patients have had fewer risk factors for neuroleptic malignant syndrome? An interesting facet of neuroleptic prescribing patterns at our hospital was that although physicians tended to prescribe more high-potency drugs (which might cause a higher frequency of neuroleptic malignant syndrome), the doses of the antipsychotic drugs they prescribed were quite modest. Our observation of a low prevalence of the syndrome, coupled with the tendency to use low daily doses of neuroleptic drugs, seems to confirm evidence suggesting that higher drug doses predispose to a greater likelihood of developing neuroleptic malignant syndrome (5).

Keck et al. (6), who conducted the only other published prospective survey of neuroleptic malignant syndrome of which we are aware, did not list the average daily exposure to neuroleptics at their institution. They did, however, note that half of their neuroleptic malignant syndrome patients had been receiving lithium along with an antipsychotic agent; it is conceivable that this joint exposure represents an additional risk factor. Alternatively, there could be other, as yet unidentified factors that might explain the higher rate of neuroleptic malignant syndrome which Keck et al. found.

Other than the survey by Keck et al., the literature contains only retrospective estimates of neuroleptic malignant syndrome, which are subject to the inaccuracies and distortions inherent in "looking backward." Our survey system was precise enough to avoid missing any cases of neuroleptic malignant syndrome. Our heightened interest in this condition, however, probably avoided false-positive diagnoses by directing attention to differential diagnosis. Thus, as Levinson and Simpson (7) have emphasized, extrapyramidal signs and fever in patients taking neuroleptic drugs can represent a heterogeneous mix of pathology, which could have inflated retrospective estimates with false-positives.

Despite the modest prevalence of neuroleptic malignant syndrome shown by our study, clinicians must remain aware of this serious condition, with its potentially lethal complications. Attention is best focused on the differential diagnosis of fever, extrapyramidal reactions, and altered consciousness in patients taking antipsychotic medications.

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Book Forum

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CHILD PSYCHIATRY

Manual of Clinical Child Psychiatry, *edited by Kenneth S. Robson, M.D. Washington, D.C., American Psychiatric Press, 1986, 312 pp., $29.95 (spiral-bound).*

The beginning of a child psychiatry fellowship is often regarded as a stressful time. Issues of professional identity are inherent in any such transition. At one time, new fellows could at least be consoled by the reassurance that their work would consist of applying familiar skills and perspectives, mostly psychodynamic, to a younger population. Now, however, although child psychiatry's traditional strengths remain as valuable as ever, they are accompanied by a proliferation of new knowledge. Trainees must rapidly master a large repertoire of material unique to the specialty and apply it to an often unfamiliar population. Many of us do not really know children well when we begin.

Manual of Clinical Child Psychiatry addresses this transition. This book is described in the preface as a "working manual for fellows in child psychiatry." Robson and his associates, all well-regarded clinicians, have condensed a diverse mass of material into a compact text. It is uniformly readable and well organized, and its contents are extraordinarily accessible. None of the essays in this book is exhaustive, but all will enable the new fellow to begin work in a thoughtful fashion, informed by contemporary standards of practice.

The first section, Diagnostic Assessment, begins with a brief review of the developmental perspective of diagnosis, followed by a very helpful treatment of the practical aspects of the initial interview. This chapter, written by Robson, typifies the authoritative, succinct, and pragmatic nature of the book. This section also contains chapters on physical and neurological examinations and psychological testing and includes a summary by Sarma of his useful Examination for Minor Neurologic Signs (EXAMINS).

The second section, Approaches to Treatment, contains an overview of individual, group, and milieu psychotherapies and a fairly comprehensive introduction to child psychopharmacology. These essays will not in and of themselves convey expertise, but they can constructively inform the fellow's self-teaching during a critical period of professional development. They may also impart some confidence. Particularly useful are the chapters on emergencies and sexual abuse and rape.

The final section addresses Consultation and Related Clinical Problems. The contents of such a section must necessarily be arbitrary, and readers may disagree with the editor's choices. For example, this section provides little on educational consultation and makes no mention of education evaluation itself. A more detailed discussion of pervasive developmental disorders, whose presentations are often confusing to beginners, might well have been included. Far more important than any individual quibble, however, is the appropriate emphasis the section gives to the necessity of child psychiatry's interaction with other disciplines and institutions. All of the topics covered, including forensic psychiatry, adoption and foster care, infant psychiatry, and genetic issues, are certainly germane to clinical practice in child psychiatry.

This book will not only assuage the anxiety of new trainees but also positively influence their professional growth. It is unique in its scope and mission, and I predict that it will become a highly regarded presence in our profession for many years. I would also recommend it to general psychiatrists, pediatricians, and other professionals as an introduction to the breadth of contemporary child psychiatry.

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Middle Childhood: Development and Dysfunction, *by Melvin D. Levine, M.D., and Paul Satz, Ph.D. Baltimore, University Park Press, 1984, 501 pp., $40.00.*

The middle childhood years (approximately ages 6–12) have received less systematic study than other developmental periods, except for studies of children with hyperactivity and conduct disorders, which are problems not easily ignored. In part, this neglect reflects relative harmony among various elements. Middle childhood does not have the upheaval accompanying the rapid physiological changes of early childhood or adolescence; it is a time of relative compliance with the guidance of parents and other adults.

This volume successfully fills a gap among books describing development and its disorders during these years. Psychoanalytic descriptions of development during middle childhood have emphasized the internal accommodations required as the child enters the social world outside the family: the formation of a conscience, the development of psychological defenses that enable the child to delay impulses and resolve conflicts, and the nurturance of cognitive and physical skills and the capacity to adapt personal goals to group participation. Although educators have charted the abilities of children to learn during this period and have attempted to devise optimal methods of instruction, descriptions of the development of other fundamental capacities (language, attention, motor function) and related disabilities during middle childhood lagged behind. During the past 15 years a body of research on these topics has been generated that awaits incorporation into our general understanding of middle childhood. This book is a long step in that direction.

The editors are successful in building a more unified concept of development in a particular subgroup of common childhood disorders, the attentional and behavioral disorders of childhood, and the specific corresponding developmental disabilities. They do not attempt to describe all dimensions of middle childhood development or to review the full range of psychiatric disorders of this period. The number of children afflicted with problems in attention, learning, behavior, or motor development justifies the decision to limit the discussion to these topics.

The very fine preface describes the centrality of middle childhood in contrast to its relative neglect. The authors give a good rationale for their focus on high-prevalence, low-severity disabilities. They raise essential questions about impediments to distinguishing among these disabilities, and the authors' realistic, nondogmatic attitude toward diagnostic problems is a strength of the book. There is no overview chapter that ties the various threads together at the beginning or end of the volume. Perhaps this is a good decision, indicating that the enormous amount of research presented in the chapters must be digested and extended before a new synthesis can be made.

The introductory section on developmental patterns contains well-organized summaries of topics that prepare the reader for development of the themes in later chapters. For example, in this part there are excellent chapters on memory and attention by Hagen and cognition and language by Palermo.

Those interested in the study of attentional function and its disorders will find chapters on these subjects by Hagen, Levine, Taylor, and Kinsbourne. Hagen explores the development of memory and attention as a necessary antecedent to learning. Levine discusses problems in children who either cannot or will not pay attention, using the terms "inattention" and "unintention" to describe these clinical phenomena. Taylor's chapter, "Medications and Their Effects," is a consideration of the use and limitations of stimulant medication in children, reviewing research on efficacy and side effects rather than attempting a definitive review of the literature on stimulants. Kinsbourne's chapter on diet therapy for hyperactive children is an intriguing account of subject matter not represented prominently in textbooks.

A series of chapters describe learning and reading and their respective disabilities. Meltzer's chapter, "Cognitive Assessment and the Diagnosis of Learning Problems," provides a good conceptual overview. Levine's chapter, "Cumulative Neurodevelopmental Debts," demonstrates how deficits in specific processes can impair learning in middle childhood, undercutting the capacity for work as the child enters adolescence. The specification, explanation, and organization of these specific processes gives the reader the tools to more accurately describe problems in learning, which in turn generates useful prescriptions for remediation. The search for predictors of learning problems in preschool children has been a complex undertaking, and a chapter by Palfrey and associates reviews both pitfalls and emerging suggestions for preventive services. A chapter by Spreen rounds out this perspective by addressing the often unfavorable outcome of learning disabilities in a group of patients followed into adolescence and adulthood. A chapter on minor motor impairments by Denckla is a gem, summarizing the history of research on the clumsy child, a subject that is a source of confusion for clinicians.

The relationship of behavior problems to disorders of learning and attention in children is the focus of both controversy and research. Offord presents an illuminating phenomenologic description of antisocial disorders and a review of possible etiologic factors. In a very useful chapter Rutter surveys the relationships of family, social, and educational factors to childhood psychopathology, providing a stimulus for better targeted research design in studies of these commonly invoked influences. O'Leary and Emery investigate marital discord as an etiologic agent for childhood behavior disorders, examining its differential impact on clinic and nonclinic populations. Needleman reviews neurotoxins (e.g., lead, alcohol, mercury) as neglected factors in the pathogenesis of developmental and behavioral disorders. Needleman's important studies are a useful context for understanding methodological problems in this sector of research. Silver's chapter, "Psychotherapy With Children With Developmental Dysfunctions," provides an enlightening discussion of the reasons for the paucity of research on psychotherapy for these children, followed by a description of the indications for psychotherapy and the actual techniques used.

In summary, *Middle Childhood: Development and Dysfunction* successfully presents thoughtful discussions of vital developmental processes of middle childhood and emerging models of psychopathology. Its strength is the fresh approach to phenomena that call for multifaceted assessment. We recommended it—especially for child psychiatrists interested in a neurodevelopmental view of middle childhood and its disorders.

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Psychopathological Disorders of Childhood, 3rd ed., *edited by Herbert C. Quay and John S. Werry. New York, John Wiley & Sons, 1986, 660 pp., $39.95.*

This third edition of Quay and Werry's work is an updated version of a classic text. Virtually all of the chapter authors are eminent researchers in child psychopathology, and their contributions generally elucidate the body of empirical research in their chosen areas. The text would be useful, perhaps even indispensable, in an advanced undergraduate course where the goal was to give students a panoramic overview of childhood psychopathology. One could use this text as a jumping-off point for a closer examination of individual topics that were considered of special interest. And the material covered in this book would provide an invaluable update for clinicians.

Most of the authors in this edition have contributed to the book in its previous editions, and this may account for a greater coherence than is typically the case with an edited volume. There are seven chapters on classification and individual disorders, three chapters on biological, familial, and cultural correlates of childhood psychopathology, and seven chapters presenting an overview of assessment instruments and a variety of standard treatments. The authors have followed similar topic outlines, which unifies the topography of chapters in similar areas.

Any sense of disarray and uncoordination in this book actually reflects the state of the field rather than the disabilities of this set of authors and editors. It is worth emphasizing that, to a substantial extent, *DSM-III-R* has made outmoded an entire literature on diagnostic categories. Like the proverbial blind men, child researchers are still groping around the different parts of the elephant. This book gives us a good sense of the individual parts, but the big picture is obviously still elusive. One hopes that by the time the fourth edition of this volume and of the *Diagnostic and Statistical Manual* appear, we shall be able to step back and view the beast in its entirety.

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TEXTBOOKS

The Medical Basis of Psychiatry, *edited by George Winokur, M.D., and Paula Clayton, M.D. Philadelphia, W.B. Saunders Co., 1986, 579 pp., $60.00.*

Preceded by the excellent reputation of its editors, this book presents in an almost impeccable format an abundance of the hard data so sorely needed by our discipline. The opening statements of the preface leave no doubt about the volume's philosophy: "Psychiatry is a branch of medicine and a psychiatrist is a specialist in that field. . . . A psychiatric illness is simply a medical illness with major emotional and behavioral aspects." The editors are not interested in the "psyche" but in specific diagnosis of specific psychiatric illnesses; psychosocial factors and psychotherapy are discussed only if they are considered relevant to the etiology or the management of the described medical (psychiatric) entities. After this emphatic preface, there are 33 chapters by 37 contributors divided into four sections.

The book has a novel addition, "editor's comments" in the middle of some chapters (I counted eight), which seems intended to expand the text with relatively new and pertinent data. In addition, in describing the organization of sections and chapters, the editors assert that "the best way to present the material is to describe the clinical entities first," followed by symptom clusters and other "specific kinds of circumstances." I think that this approach, perhaps more than the content itself, will create a lively reaction among the book's readers. If that is the case, it will not be because of a mythical battle between innovation and conservatism but probably because of differing philosophies about the way medical students and psychiatric residents should learn the tools of our trade.

Section one, Syndromes—Adult, includes 17 chapters. One can surmise that the topics of these chapters represent the most common and perhaps best documented types of psychiatric disorders among adults. (Incidentally, the editors equate disorders with diseases, a view that is, at best, debatable.) Here one finds true syndromes such as the organic brain disorders mixed with relatively well-established entities such as schizophrenia and bipolar depression, plus different kinds of neuroses (and it is interesting that Winokur and Clayton rescue this term so dear to and so sorely missed by psychoanalysts), broad categories such as alcoholism and drug abuse, and narrow ones such as antisocial personality. I wonder if the chapter "Special and Unusual Psychiatric Syndromes" should have been placed in section three or four rather than here.

Be that as it may, most chapters are written authoritatively and cogently. The text in each chapter follows the sequence accorded to nosological categories in general medicine textbooks, namely, definition, etiology and pathogenesis, epidemiology, pathology, clinical picture, clinical course, laboratory findings, differential diagnosis, and treatment. Although all of the chapters are good, some fulfill their objectives (to provide a coherent update of current knowledge and to make clear and cogent statements about otherwise controversial issues such as etiology and management) better than others. I liked chapter 2, "The Amnestic Syndrome," chapter 6, "Schizophrenia," chapter 8, "Obsessive-Compulsive Neurosis," chapter 10, "Anxiety and Phobic Disorders," chapter 12, "Paranoid Disorders," and chapter 13, "Alcoholism." Because of personal preferences, I read with particular interest chapters 4, 5, 7, 12, and 15. The danger of duplications became immediately apparent reading chapter 4, "Bipolar Illness," and chapter 5, "Unipolar Depression." Although the trend was toward asserting their autonomy (thus, separate chapters) the content showed an inevitable overlapping. A commendable emphasis on the intricacies of clinical assessment is the main strength of chapter 4. I was appalled, however, that the name of the originator of the unipolar-bipolar distinction is misspelled as Leonard (it should be Leonhard) in several parts of the chapter, including the editor's comment, and is omitted from the reference list. There is no mention of the phenylethylamine hypothesis in the pathogenesis of the disorder (1) and no mention of the better validation of the concept of endogenous depression by use of the dexamethasone suppression test put forth by Zimmerman et al. (2). Studies on the interepisodic behavior of bipolar patients (3) are omitted, and a statement is made that ECT has not been used in rapid cycling disorder, which is not necessarily true (4). Furthermore, reading a chapter such the one on unipolar depression shows how much more remains to be done in trying to disentangle the complex web of these disorders. The renaissance of the neurotic-reactive concept, promulgated by Winokur himself, collides with the notion of depressive personality, and the autonomy of unipolar depression (described mostly as a spectrum-like process) is difficult to understand. The issues of secondary depression and so-called induced depression, as distinguished from primary and secondary depression, make the reader feel that he or she is dealing with entirely different groups of patients even though similar labels are used to designate them. Although the treatment section is very good in general, it is surprising to find no mention of the second-generation antidepressants, only a few lines on the dietary restrictions for those taking monoamine oxidase inhibitors, and vague references to more specific management issues.

The chapter on schizophrenia is extremely well written, particularly in its treatment of symptomatology, course, and outcome, but it should have included explications of the expressed emotions concept (5) as well as the psychosocial approach so well put forward by Hogarty et al. (6). It is good that the two chapters on organic brain syndromes pay tribute to Lipowski's seminal contributions. It is not good, however, that the chapter on the amnestic syndrome appears to advocate pneumoencephalography, an obsolete diagnostic procedure. There is no clear explanation of why schizoaffective and schizophreniform disorders have been grouped together in chapter 7 when the two disorders are discussed separately throughout. The duet of somatoform and dissociative disorders in chapter 9 quickly evolves into a remake of the conversion and dissociative reactions described in *DSM-II*. There is poor information regarding the longitudinal course of anorexia and bulimia in chapter 11, and chapter 13 on alcoholism omits the rich contributions of Latin American students on the matter, particularly those from Chile (7). Chapter 14, "Drug Abuse," does not mention the current "crack" epidemic, probably because of its relative newness. The list of folkloric or psychocultural syndromes in chapter 7 omits *susto*, also described by Latin American authors (8, 9).

The four chapters that form section two, Child Psychiatry, discuss conduct disorders and hyperactivity, major affective disorders in children and adolescents, infantile autism and schizophrenia in childhood, and emotional disorders in children. I perceived here an emphasis on behavioral approaches to the management of conduct disorders and hyperactivity and a lack of emphasis on the detailed neuroleptic management of schizophrenia in childhood.

My problems in understanding the book's structure grew by reading section three, Symptom Clusters. Why were chapters as general as "Diagnosis in Psychiatry and the Mental Status Examination" (chapter 22) as well as general symptom-based chapters such as "Mood Disturbances" (chapter 23), "Anxiety Symptoms" (chapter 24), and "Thought Disorder" (chapter 25) left to occupy the third section of the book rather than serving as true introductory chapters on psychopathology in the best Jaspersian tradition? The pragmatic answer given in the preface ("One starts to learn by seeing patients and then categorization occurs") does not correct the impression that we are moving backwards from admiring the dazzling finished product to the boring but indispensable task of knowing its constituents or even the raw material with which artists, scientists, and teachers (who, of course, have a lot in common) usually start their work. This approach may be good for window-watching consumers but not for future professionals. In any event, most of the chapters in this section are masterfully written. Yet, I would have liked to see chapter 22 complemented by a good neuropsychiatric evaluation, as described, for instance, by Gross (10), in order to do justice to the medical basis of the book's philosophy. Chapter 23, "Mood Disturbances," cannot avoid the duplications alluded to for section one but provides a good review of the complexities of the spectrum notion. Incidentally, for Brockington et al. (11) the distinction between cycloid psychosis and schizoaffective disorders is clear, so they are not one and the same thing, as a statement in this chapter implies. Chapter 24 provides a good justification for the inclusion of an organic anxiety disorder in *DSM-III-R*. Chapter 25 includes provocative ideas, such as the consideration of the hallucination as a thought disorder and the fascinating linguistic distinctions between schizophrenic and manic thought disorders. Chapter 26, "Phenomenology of Coarse Brain Disease," would have definitely benefited from some figures and tables, even though this does not take anything away from the exceptional level of the text. The same can be said of chapter 27, "Motor Behavior," and chapter 28, "Personality Disorders." It is clear, however, that only antisocial and perhaps borderline personality disorders are well enough studied, so it would be a mistake to think that the biochemical abnormalities presented here apply to all the other personality types that are found.

The last section, Special Areas, includes a scholarly work entitled "The Neurobiological Basis of Psychiatric Illness" that is one of the best presentations of neurotransmitter chemistry I have ever read. "The Genetics of Psychiatric Disorders," chapter 30, is also notable. Chapter 31, "Use of the Laboratory in Psychiatry," does not fulfill the reader's expectations because, for instance, it devotes only one page to visual imaging techniques and presents a duplication of the section on neurotransmitters. Chapter 32, "Epidemiology of Psychiatric Illness," is one of the most thorough and accessible of the whole book, and chapter 33, "Suicide and Attempted Suicide," is a good summary of this special area (not so specialized, however, as to warrant exclusion from either section one or section three).

In short (is it possible to make short statements in examining a book of this scope and breadth?), one can say that *The Medical Basis of Psychiatry* has laudable intentions, a granitic philosophical foundation, the invaluable contribution of researchers writing on their own work, openness to nonmedical contributions, and adequate balance to appeal to readers of many persuasions and disciplines. On the minus side, I found in this volume the unequal weight and consistency of most multiauthored volumes, lack of uniformity in the formal presentation of the chapters, a controversial structure and organizational style, and a few but important errors of commission and omission. It will be a much-used reference book as well as a basic text to be read before consulting more narrowly focused volumes that reflect modern trends in psychiatric knowledge (12). Obviously, the editors must be ready to introduce improvements in future editions and thus reach new heights in public acceptance and recognition. In so doing, they (who profess an overriding interest in what is inside the *Leviathan* of psychiatric knowledge but not in *Leviathan* per se) will surely not forget that the very allegory they have chosen encompasses, even in its meandrous interiors, the notions of rigidity, absolutism, and enormity, approachable only by means of a constructive critical attitude and an objective recognition of psychiatry's own accomplishments and limitations as a scientific discipline.

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The American Psychiatric Press Textbook of Neuropsychiatry, ***edited by Robert E. Hales, M.D., and Stuart C. Yudofsky, M.D. Washington, D.C., American Psychiatric Press, 1987, 463 pp., $55.00.***

Drs. Hales and Yudofsky have tapped the talents of many of the best researchers in the United States to produce a finely crafted textbook covering a long-neglected area—neuropsychiatry. Neuropsychiatry is that murky interface between psychiatry and neurology where patients have symptoms which overlap the two medical specialties and which seem ill-served by either specialty. In the introduction to this book, Shervert Frazier notes that Parkinson's disease is the prototypic example of a neuropsychiatric disorder "wherein motor changes (bradykinesia) and mood changes (major depression) are both likely to be derivative, in part, of a disordered catecholamine system." *The American Psychiatric Press Textbook of Neuropsychiatry,* one hopes, will help bridge the gap between the two specialties.

The book combines the efforts of 42 contributors who are noted experts in subjects related to neuropsychiatry or promising young investigators. Despite occasional lapses, the book is well organized, visually inviting, and, because of its large, near-folio size, easy to grasp and hold. One does not need a magnifying glass to read this book.

The breadth of material covered is substantial. For easy consumption and use, it is divided logically into four sections: Evaluation and Basic Principles, Organic Mental Disorders, Neuropsychiatric Disorders, and Treatment Issues in Neuropsychiatry.

The first section begins with a chapter by Michael Alan Taylor, Frederick S. Sierles, and Richard Abrams, who cover the neuropsychiatric evaluation and incorporate much of what they have refined over the years and presented in their book *General Hospital Psychiatry* (1). Brain imaging and laboratory tests, neuropsychological evaluation, and neurotransmitters and neuroreceptors are discussed in well-illustrated chapters. These chapters provide the foundation for the balance of the book.

The second section is devoted to descriptions of major mental disorders. Michael Wise, Troy Thompson, and G. Alan Stoudemire contribute highly readable chapters on delirium, dementia, and selected organic mental disorders (e.g., organic mood syndrome and organic hallucinosis), respectively. Wise stresses a thorough evaluation of delirium to determine etiology and uses clever mnemonics to help the clinician, including WHHHHIMP and I WATCH DEATH. The remaining chapters in this section cover alcohol- and other substance-induced organic mental disorders. The chapter on substance-induced disorders does not follow the same format as the others: it presents case histories illustrating each type of substance abuse disorder (including neuroleptics as a substance of abuse). Some clinicians may find the format distracting, but the material is current and the case reports are valuable.

The third section presents 12 chapters on the subjects of neuropsychiatric aspects of brain injury, cerebral vascular disease, epilepsy, headache and facial pain, sleep disorders, degenerative diseases, metabolic diseases, endocrine disorders, vitamin deficiency states, infectious and inflammatory diseases of the CNS, brain tumors, and disorders of childhood and adolescence. These chapters are uniformly excellent, up-to-date, and liberally referenced. They cover information that clinicians need ready access to for these neuropsychiatric disorders—classification, epidemiology, etiology, differential diagnosis, psychiatric manifestations, clinical evaluation, and treatment.

The last section of the book is concerned with treatment issues in neuropsychiatry, specifically, psychosocial interventions, drug treatment, rehabilitative efforts, and forensic aspects. These chapters provide useful guidelines for treating the patient with neuropsychiatric conditions. David Forrest provides common-sense recommendations for the psychosocial management of different syndromes, as does Steven Dubovsky for the psychopharmacologic management of neuropsychiatric disorders.

The book has so many positive aspects that it is easy to overlook its imperfections. The book is multiauthored and, as a result, several chapters overlap, some are poorly written, and important material is occasionally omitted. For example, three chapters include discussions on epilepsy and its possible effects on personality and emotions. Propranolol was not mentioned in the chapter on drug treatment but is casually referenced in the chapter on cognitive rehabilitation. Discussion of stimulants as a treatment of depression in the medically ill is omitted altogether. Although headaches and facial pain are covered, chronic pain of other origins is not. One chapter is particularly poorly written—in one random paragraph the irritating phrase "the fact" occurs five times, references are incomplete, and some questionable information is presented. Other criticisms are minor. For example, although the chapter on endocrine disorders is well written, it is more or less reprinted from another text and relies on reviews rather than primary sources for its references. Additionally, the authors make the unsupported recommendation that depressed patients who fail to respond to somatic treatment should have a thyrotropin-releasing hormone stimulation test.

Needless to say, in a large volume of this nature imperfections are unavoidable. On the whole, these are rather minor distractions and do not detract from the overall mission and value of the book.

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American Handbook of Psychiatry, 2nd ed., vol. V[illegible]I: Biological Psychiatry, *edited by Philip A. Berger, M.D., and H.K.H. Brodie, M.D.; Silvano Arieti, M.D., Editor-in-Chief. New York, Basic Books, 1986, 1,118 pp., $75.00.*

This volume of the *American Handbook of Psychiatry* is a wonderful new addition both to the *American Handbook* series and to the literature on biological psychiatry. This is an extensive text which has more than 1,000 pages and 36 chapters. Many of the chapters include extensive bibliographies and data from the most recent articles in biological psychiatry.

The *American Handbook* (this volume I think has outgrown the term "handbook" and should better be termed an "armbook" or a "wheelbarrow book") is organized into four major sections. The first section, The Neurobiology of Psychiatric Disorders, includes six chapters ranging from chemical neuroanatomy to neuropeptide or neuroendocrine involvement in psychiatric disorders. These well-written chapters are followed by chapters on neuropathology in psychiatric disorders and the genetics of psychiatric disorders. Part two, Scientific Approaches to Biological Investigations in Psychiatry, includes chapters on animal models in psychiatry and the use of electrical potentials in psychiatric disorders as well as a wonderful description of the findings on CAT scan in schizophrenia and affective disorders. This section also contains chapters on findings based on positron emission tomography and blood flow study and the potential uses of nuclear magnetic resonance imaging in psychiatric disorders. Part three, The Biology and Treatment of Specific Psychiatric Disorders, is the largest section of this text and includes what is known of the biological etiology, pathopsychological mechanisms, and treatments of specific disorders. Although the majority of the chapters and most of the space are devoted to the schizophrenic and affective disorders, the psychiatric disorders included in this section range widely from anxiety disorders to aggressive disorders, Alzheimer's disease, childhood disorders, chronic pain, eating disorders, substance abuse disorders, and somatic disorders. The final section of the comprehensive book, Controversies in Biological Psychiatry, includes chapters on ECT, psychiatric surgery, use of laboratory tests, and ethics.

The editors of this text did an outstanding job of organizing this group of authors and editing the chapters to provide a logical and smooth transition from one chapter to the next. They point out at the beginning of the preface that "psychiatry is a biomedical science." This book is clearly a testament to the veracity of that statement as well as to the strength of the empirical method in psychiatry. One only has to look at the thousands of references cited in this textbook to grasp the enormity of the empirical work that has been going on in psychiatry for the past decade.

I was pleased to see that, in addition to presenting the state of biomedical knowledge in psychiatry, many of the chapters in this book place great emphasis on the interpretation of findings in the light of relevant methodological and theoretical issues. One cannot adequately interpret findings without understanding the theoretical framework or "perspective" from which a problem is being studied and its strengths and weaknesses. Another impressive aspect of this text is the contributing authors. It is unusual to have such a large number of authors who are preeminent investigators in the fields they describe.

The two most common problems of multiauthored texts (i.e., overlap of material between chapters and uneven styles) are largely not found in this text. In spite of the fact that there are many authors, the text is remarkably well written and flows smoothly from one chapter to the next. Although one might quibble about the exclusion of several areas of biological investigation in psychiatry, such as the neuropsychiatric disorders (although Alzheimer's disease is covered in a well-written chapter), this book is wide-ranging in its coverage of biological issues in psychiatry and in its scholarly presentation of scientific, methodological, and theoretical issues. It is also a clinically useful and informative text. Almost all of the contributing authors make a point of discussing recent findings on treatment and clinical practice.

Whatever your interests may be in psychiatry, I can highly recommend this handbook as an important source of information and reference for the underlying neurobiology, techniques, and clinical management of many psychiatric disorders.

This is the kind of book that not only impresses one with the magnitude of scientific advances in psychiatry but also boggles one's mind as to how any one human being can try to keep abreast of the rapidly expanding field of scientific knowledge in psychiatry. I am sure the next edition will be at least two armfuls.

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BIOGRAPHY AND AUTOBIOGRAPHY

Autobiographical Memory, *edited by David C. Rubin. New York, Cambridge University Press, 1986, 295 pp., $39.50.*

David Rubin is a good editor. He has taken what could have been just another symposium destined to be a book and turned it into a balanced, informative, internally referenced volume that rewards the reader with a realistic overview of the field of autobiographical memory, a recently revived branch of cognitive psychology. Rubin thinks of the book as a "tutorial on the cognitive psychology of autobiographical memory." It is that and more. The form of the book helps define the present status of the field. Rubin acknowledges in his most helpful introduction that if he attempted a definition of autobiographical memory, he would restrict the scope of the book and its participants. Thus, the authors of *Autobiographical Memory* have their own related but varied explicit or implicit definitions. Rubin believes that the field is young and that it currently contributes questions rather than an established body of data and theory.

A short historical note might help here. The field began with Sir Francis Galton (1822–1911), a botanist and taxonomist. Galton contributed classification, associations to stimulus words, and the actuarial recording of reaction times at various life phases. Then Ebbinghaus (1850–1909) stressed rote memory measured with easily verifiable experiments. Of course it was Freud's concepts of memory traces, repression, screen memories, childhood amnesia, biography, autobiography, and symbolism that dominated the study of autobiographical memory for more than the first half of the twentieth century. The soft scientific plushness of the couch and the standard of plausibility seemed to satisfy. However, experimental psychologists reached back to the work of Ebbinghaus, and the study of autobiographical memory began to be characterized by tightly drawn experiments based on theories of verbal learning.

This is where Rubin and his colleagues came to help move the field away from a reductionistic position. Description, phenomenology, and quality began to supplement quantitative measures. The intensity of an image and the context in which it was laid down have become important in determining whether it is capable of being retrieved. Although conscious retrieval strategies are emphasized, the presence of involuntary factors is also taken into account.

To an observer outside the field, such as myself, the book becomes a fascinating study of a group of serious workers rediscovering the wheel of developmental and dynamic psychology. Linton, in her interesting chapter, "Ways of Searching and the Contents of Memory," uses her own life history and various self-searching strategies to build a plausible hierarchical outline of memory categories. In remarking about the complex continuum she found between "what pours out of memory" and "what can be elicited," she remarks that "thoughts that come unbidden may be akin to the free associations used by psychoanalysts and may be a special and potentially rich field for cognitive psychologists to till."

Citing the dearth of reliable information on childhood amnesia, Wetzler and Sweeney, on the basis of carefully designed studies, announce that "childhood amnesia does exist." Then Neisser, in a systems-theory-influenced paper, "Nested Structure in Autobiographical Memory," discusses the isolated memory. Sometimes repeated experiences transform what the cognitive psychologists call "episodic" or individual memories into more general ("semantic") memory. Neisser notes, however, that "a few individual events remain accessible. One of them is usually the most recent instance of the class, but a few others may also survive in a kind of splendid isolation." Neisser calls a single memory that stands for a class of memories "repisodic" memory. Appropriately, he cites Freud's concept of screen memories as being relevant: "A screen memory seems to describe only a single and unimportant childhood episode but really represents something deeper."

In keeping with this apparent psychoanalytic innocence and the seemingly revolving door of scientific investigation, the book reflects a currently revived debate concerning the copy theory of memory, which searches for veridical reliability, versus a constructive or reconstructive view of memory which assigns importance to the feeling that an event took place over the actual occurrence of the event in contributing to the sense of self. I would have thought we had gone beyond this.

Even with these problems, this is still an important book by a group of cognitive psychologists who are interested in more than verbal learning. The book refers to Piaget's developmental concept, theories of the self and self schemata, various concepts of time (clock time versus personal and social times), the impossibility of artificially separating perception from memory, narrative theory, holism, and an ecological theory of memory that takes the temporal structure of the real, "to-be-remembered" world seriously. As I have implied, there is a realization that psychoanalytic observations may be helpful in providing hypotheses for the cognitive psychologists and in providing content that will deepen their understanding of a cognitively structured mind embedded within a complex semiotic, symbolic, perceptual, narrative, and integrative world. Also, psychodynamic therapists can learn a great deal here about the nondynamic aspects of autobiographical memory.

A pragmatic suggestion arises from reports of interesting studies of organic amnesia. Workers with elderly patients who have organic illnesses try to orient them to time, place, and environmental activity, but there is increasing recognition of how crucial reminiscence and life review are to healthy middle-aged and older persons as well as to those with organic disorders. The psychological importance of past memory is being realized. Memories evoked by old photographs and treasured objects can help to shore up one's sense of self. As Baddeley and Wilson write in their chapter, "Amnesia, Memory and Confabulations," "What these patients need to establish and maintain is not just where they are but who they are."

Autobiographical Memory is a fine and hopeful book. It points to increasing multidisciplinary cooperation and to the possibility that the rigor and experimental expertise of cognitive psychology can lend itself more and more to the challenge of proving scientific validity to the dynamic and symbolic psychotherapies.

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Freud as an Expert Witness: The Discussion of War Neuroses Between Freud and Wagner-Jauregg, *by K.R. Eissler. Madison, Conn., International Universities Press, 1986, 422 pp., $40.00.*

In the bitter aftermath of World War I in defeated Vienna, a chorus of complaints about the conduct of the war included allegations that wounded soldiers had been improperly treated, even mistreated. As a result, a commission of inquiry was set up to investigate the care received by soldiers with war neuroses in the psychiatric division of the Vienna General Hospital. The division was under the supervision of the eminent professor Julius Wagner-Jauregg (later a Nobel Prize winner for his work on the malaria treatment of paresis).

Freud as an Expert Witness describes the 2-day hearing on these accusations. Sigmund Freud was engaged as an expert witness, and although he largely exculpated Wagner-Jauregg, his testimony led to a debate between the advocates of psychoanalytic methods and most military psychiatrists, whose chief modality of treatment was electrical faradization. Basic to the controversy was disagreement about the nature of the pathology of the many soldiers who displayed disorders of motility (tremors, astasia-abasia, stiffness, weakness, paralysis, etc.). These disorders were usually but not always the result of exposure to combat conditions. The principal accuser of Wagner-Jauregg at the commission hearing was Walter Klauders, an Austrian officer who, following exposure to a bomb blast early in the war, developed a set of symptoms that seemed bizarre. He was relieved of active duty and, toward the end of the war, sent to the Vienna General Hospital. He later charged that his treatment there, particularly faradization but also isolation and forced ambulation, had been cruel and inappropriate. Dr. Eissler interviewed Klauders at the age of 80 about his recollections of the episode.

The motility disturbances of the soldiers were explainable on three different grounds. They could be the result of difficult-to-detect organic lesions, they could be manifestations of traumatic hysteria, or the soldiers who exhibited the symptoms could be malingerers. The bulk of this book is devoted to the pros and cons among these various possibilities. The organic hypothesis is discarded, although Eissler seems reluctant to do this in the case of Klauders, relying on some rather minor neurological abnormalities found by the eminent German neurologist Dr. Wilhelm Erb. This leaves neurosis and malingering as the chief etiological candidates. Wagner-Jauregg, his assistants, and most other military psychiatrists considered malingering the main operative factor, although Wagner-Jauregg recognized, as Eissler does not seem to, the fluid boundaries between neurosis and malingering. Freud minimized the importance of malingering and so, emphatically, does Kurt Eissler, but his long discussion of malingering, although interesting, is not entirely clear. He considers conscious feigning of illness to be malingering only if the motive cannot be seen in a moral context, but he also believes malingering to be an illness in itself and thus presumably free from moral judgment.

Eissler comes down very strongly on the side of Freud and the other psychoanalytic observers in their contention that the motility disturbances were neurotic, caused by unconscious conflicts between duty and self-preservation. Eissler is also critical of the Austrian and German military psychiatrists, sometimes with good reason, although one could suspect that their vehemence against Freud and his method was partly the result of an indignant feeling that they, who were directly involved in the treatment of a large and recalcitrant group of disabled soldiers, were being disparaged by Freud, who had no direct contact with the case material. It appears that the extensively used faradization was quite successful, at least in the early days of the war before widespread mutinous discontent set in. Freud explained this as the result of a shifting of unconscious forces, but the military psychiatrists seemed to accept its punitive role (the soldiers were scared back to at least limited duty) along with an obvious element of suggestion. Freud extolled, and so does Eissler, the apparent success of the more humane treatments used by a few psychoanalytically trained military psychiatrists (e.g., Simmel) who combined a modified psychoanalytic method with hypnosis. However, Eissler somewhat contradictorily notes later that almost any method of treatment of war neuroses had a good deal of success if the soldiers were returned to limited noncombat duty. It was also true that all methods were less effective later on in the war.

Freud as an Expert Witness is a rather curious production. Dated 1973, the English edition was apparently completed in 1976, but the publication date for the volume is 1986 and the German version was published in 1979. The literature and controversies of the World War I period are covered thoroughly, perhaps excessively so. The quality of the writing is marred by a considerable amount of repetitiousness and a tendency to go off on excursions of only tangential interest to a present-day readership. There are nine appendixes of varying degrees of relevancy.

What is the value of this book for a psychiatrist today? It will be of particular interest to those with a historical bent, and the observations of Kurt Eissler, although sometimes idiosyncratic (as when he states as gospel the generally discredited notion of a specific psychic energy), are often salty and valuable.

There is also some value in contrasting the concerns of psychiatry of the World War I period with our concerns during and since World War II. It is ironic that there were moral and legal sanctions operative in all of the major World War II armies against measures such as faradization, isolation, and the use of asafetida but that war also saw infinitely more evil inhumanities inflicted by Nazi military doctors on captives. Can a rationalizing scientism be seen as an underlying factor in both instances?

Another issue of interest is that of dual loyalty: can psychiatrists properly serve the interests of both the military and their patients? This issue is currently widely acknowledged but certainly was not a matter of concern in the authoritarian days of World War I. However, in the final appendix in the book, a 1975 article by Peter Buttner takes Freud to task on these very grounds because of the fundamental incompatibility between the individualistic aims of psychoanalysis and its use to return soldiers to the inhuman environment of war. In his book, Eissler defends Freud against this stricture, but one can detect a note of discomfort in his argument.

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Walter B. Cannon: The Life and Times of a Young Scientist, *by Saul Benison, A. Clifford Barger, and Elin L. Wolfe. Cambridge, Mass., Harvard University Press, 1987, 520 pp., $30.00.*

For those of us who spend our working hours doing psychotherapy, reading modern biographies may often seem like more of the same. Not so with this old-fashioned book, which spares us any deep insights into the soul of the subject. Walter Cannon, a physician-researcher who headed the physiology department at Harvard Medical School in the early twentieth century, is presented in terms with which he himself might have been comfortable. We meet here with a good and honorable man who did good things.

The reader will not find a search for the deeper and darker motivations of scientists such as we have come to expect since James Watson's pioneering *Double Helix* (1). Cannon's political infighting at Harvard is glossed over and his opponents receive short shrift. Although Cannon clearly suffered from bouts of depression so severe that his wife concluded he had committed suicide when he failed to come home one night, the authors discuss this problem only in passing. And Cornelia Cannon, the wife in question, is presented as Cannon saw her, the perfect Victorian helpmate. The authors seem unaware of the extent to which they may be merely mirroring Cannon's fantasies in describing Cornelia.

The lack of psychological sophistication in this book is paralleled by an absence of historical sophistication. Cannon's loss of religious faith is not set in the context of late-Victorian America, in which such crises were commonplace. Nor is his idealization of his marriage, with its exaggerated division of gender roles, placed, as it should be, in a larger history of sex roles and family. The struggles of the Harvard Medical School to reform itself are presented as unique even when they might have served better as an interesting case study in the history of professionalization, a subject that historians and sociologists have explored widely. Similarly, the battle between scientific researchers and antivivisectionists is left floating as an isolated issue when it needs to be anchored in cultural history. The notes further demonstrate what is evident in the text—the authors are unfamiliar with key works of American social and intellectual history produced in the last decade. Therefore, they write as though the history of science is simply a chronology of great discoveries, when in actuality it must be an attempt to understand how any era's "science" is determined by its cultural milieu.

Despite these problems, however, this is a fine old-fashioned biography. The young man's difficulties—his mother died when he was 10 and his father was inattentive and eccentric—are presented sympathetically. At Harvard, Cannon was doubly an outsider, both as a Midwesterner and a scholarship boy, and we find lively discussions of his battles there. Once Cannon became established, he did important research both on the gastrointestinal system and on the body's response to emotional stress. He was an innovative scientist and methodologist, a pioneer in the use of X-rays for physiological research. His effort to establish the case method at Harvard and his defense of the use of animals in research will arouse the sympathy and interest of most physicians.

The authors do a good job of setting Cannon's labors in the context of the history of scientific research, narrowly construed. They make it easy for us to understand what he was seeking, what the methodological problems were, and how he solved them. They write clearly, making good use of direct quotes, so that the book is both lively and scholarly.

One wishes that they had made it more clear to us why we should want to read about Cannon more than any of a dozen other scientists. It would also be good to know why they stop the book when Cannon went to war in 1917 and whether they plan a volume on the rest of his life. These gaps typify the book's approach, which is to tell the facts rather than to ponder their significance. Still, straight facts have their charms, and if after a day of struggling with conflicts and ambiguities you long to refresh yourself with a simpler vision of life and also to receive some instruction, this might be just the biography to choose.

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STRESS AND STRESS DISORDERS

The Hyperventilation Syndrome: Research and Clinical Treatment, *by Robert Fried. Baltimore, Johns Hopkins University Press, 1987, 165 pp., $25.00.*

It is most unusual to have a fulfilling monograph on a single subject dedicated to the hyperventilation syndrome. Of course, the reader will necessarily learn or relearn the basic concepts of respiration, acid base, and the alterations attending to excitement, breathlessness, anxiety, and an elaborate readjustment to maintain stability.

Following an introductory chapter on the anatomy and physiology of the respiratory system, the author describes the physiology of the upper respiratory system, including the airway passages. He cites an association with migraine and then directs attention to the lungs and their intactness and relation to the thoracic cavity and its chemistry. He identifies both the normal and the abnormal complications that often relate to interference in other organ systems, including the respiratory control centers of the brain and the pneumotoxic center of the pons medullary and the respiratory centers of the cerebral cortex. Each mini-section of the respiratory system is clearly described anatomically and physiologically.

The third chapter addresses functional relationships between pulmonary, cardiovascular, nervous system, and EEG changes. Much of the mechanism of hyperventilation relates to a secondary disruption of normal physiology, sometimes resulting in seizures and other organ disturbances. Another chapter identifies the relationship between hyperventilation and mental disorders such as anxiety and panic disorders as well as anorexia, bulimia, and syndromes related to obsessive-compulsive disorder. A brief chapter addresses the pharmacological treatment of hyperventilation. Other methods include yogic techniques, breathing, transcendental meditation, behavioral treatment with imagery, and biofeedback. There are several appendixes outlining breathing retraining, including 21 references that would be quite useful.

In summary, this monograph is carefully structured and succinct enough to convey maximal information in a clear and concise form.

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Trauma and Its Wake, vol. II: Traumatic Stress Theory, Research, and Intervention, *edited by Charles F. Figley. Ph.D. New York, Brunner/Mazel, 1986, 336 pp., $40.00.*

In 1936, while at McGill University, Hans Selye injected extracts of cattle ovaries into rats to see whether their organs would display unpredictable changes. Very soon he found that all toxic substances, irrespective of their source, produced the same pattern of response: 1) the cortex of the adrenal gland became enlarged and hyperactive, 2) the spleen, lymph nodes, and lymphatic structures shrank, and 3) deep, bleeding ulcers appeared in the stomach. This reaction, described in *Nature* as a "syndrome produced by diverse noxious agents," became known later as the general adaptation syndrome or the biological stress syndrome.

Since Selye's discovery, several wars have devastated countries and killed millions of people. Countless disasters, both manmade and natural, have destroyed thousands of lives. Rapists, murderers, and terrorists have made victims of all of us. We have gone through four versions of the *DSM* and thousands of pages describing stress, trauma, and their sequelae and still we are unsure of the exact role of stress in the genesis of emotional disorders (1).

This second volume of *Trauma and Its Wake* is the eighth book in the Psychosocial Stress Series published by Brunner/Mazel. The series is edited by Dr. Figley, and the editorial board looks like Who's Who in the area of posttraumatic stress disorder (PTSD). The book is divided into three sections: Theory, Research, and Intervention. These include chapters by such scholars in the field as James L. Titchener, John Russell Smith, Jacob D. Lindy, and Susan D. Solomon.

Section one starts with a nice short chapter by Titchener on the posttraumatic decline. He describes what happens when a person develops a chronic PTSD. In the same section Smith tells us about sealing over and integration in a fine chapter with glimpses of literary brilliance.

Section two, the weakest in the book, contains a chapter by Silver and Iacono entitled "Symptom Groups and Family Patterns of Vietnam Veterans With PTSD," which, despite its wordiness and length, manages to convey a good amount of information. Another chapter worth mentioning in this section is the one written by Jenny A. Schnaier, Director of Women's Programs for the Vietnam Veterans of America, on the mental health adjustment of female Vietnam veterans.

Section three begins with Lindy's knowledgeable chapter on the psychoanalytic psychotherapy of PTSD. Two other chapters in this section worthy of mention are Solomon's on mobilizing social support networks and Wilson and Zigelbaum's discussion of the use of PTSD as an insanity defense.

The other chapters in the book are mediocre at best; two are particularly poor: "Systematic Desensitization," which draws conclusions using a very small sample of patients receiving multiple treatments, and Silver's "An Inpatient Program for PTSD: Context as Treatment," which is simplistic, wordy, polemic, argumentative, and anecdotal.

In summary, *Trauma and Its Wake, vol. II,* represents one more book in a tremendous proliferating literature on stress disorders which promises more than it delivers and which I venture to predict will have a limited readership.

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STATISTICS

The History of Statistics: The Measurement of Uncertainty Before 1900, *by Stephen M. Stigler. Cambridge, Mass., Harvard University Press, 1986, 410 pp., $25.00.*

Burton's remark, in *Anatomy of Melancholy,* about a dwarf standing on the shoulders of a giant being able to see farther than the giant himself repeatedly comes to mind when reading this book. The title aptly describes the contents. It is a history of statistics essentially up to the early work of R.A. Fisher, who revolutionized statistics early in this century and whose mark can be seen in every scientific journal. Original as Fisher's ideas were (significance tests, principle of maximum likelihood, optimality of estimators of the parameters of statistical models), they did not spring *de novo* from his forehead. The path leading to these ideas was a tortuous one, traced in detail by the author of this most interesting book.

The history starts with the principle of least squares, originated in astronomy to reconcile small deviations from observatory to observatory and later from observer to observer. This beginning is important because it fostered the idea of combining observations according to a sensible rule while explicitly allowing for their heterogeneity. A second thread, that of the measurement of uncertainty, was exemplified in the works of Bernoulli (discoverer of the binomial distribution), De Moivre, and Thomas Bayes. (Bayes's prescient paper on inverse probability, published by Price after Bayes's death in 1761, founded what is now called Bayesian statistics.)

The topic of inverse probability concerned many mathematicians, who wished to have some way to quantify the probability of the correctness or degree of truth of a hypothesis. Their treatment was not without arbitrary assumptions (a really coherent theory was not provided until De Finetti's work in the 1920s). Nonetheless, their introduction of probability concepts was important. It eventually enabled a mathematical formulation of the departure of observations from our models, allowing workers like Karl Pearson and R.A. Fisher to develop a rigorously justified method for testing models. Early ideas by Laplace on the subject of inverse probability are given a full chapter in this book, followed by an excursus on Gauss's synthesis of least squares and the concept of probable error of estimation (the forerunner of our modern concepts of confidence intervals).

Part two of the book concerns the extension of probability concepts to the social sciences (sociology, economics, and psychology) and has direct relevance for psychiatry. It was not obvious to early workers in this area that there were deep connections between the mathematics of combining astronomical, geodetic, and meteorological data (using least squares or approximations to it and invoking the concept of probable error) and the treatment of social statistics. Early work was considerably handicapped by questions about the ability of social data to form statistics, although no one questioned that astronomical observations, while differing from one another, are all measurements of the same underlying quantities. (The concept of decomposing variability into parts due to different sources of heterogeneity is really a fairly recent one.) The development of mathematical equations to describe psychophysical correlations in psychology helped pave the way for the use of statistical reasoning in behavioral science. The concept of observer error, originally described empirically in astronomy by the personal equation, was given a firm foundation with the introduction of psychophysical statistics.

Stigler argues, however, that the greatest conceptual leap was the extension of statistics to the study of heterogeneous populations by the Galtonian movement in psychology. Normal distributions, originally developed as approximate limiting forms for binomial distributions with large numbers of trials, were used in fields like astronomy to model the presumed influences of myriad disturbances acting to produce small perturbations in the value of measurements. It was Galton's insight that these same distributions, and especially their bivariate generalizations, could be used to describe wide variations in anthropometric characteristics and in behavioral traits, including such complex traits as "eminence." An illustration of Galton's quincunx, a device for mechanically demonstrating the central limit theorem for binomial variables, is given, and it reveals the depth of Galton's remarkable if nonformalized mathematical insight.

The book concludes by summarizing the transition from these early developments to modern statistics, as exemplified by Karl Pearson and his students at the Galton Laboratory, which he headed. Important steps toward formalizing the mathematics of heredity for continuously varying traits were made; the chi-square distribution was described, explored, and applied, and methods for fitting theoretical distributions to empirical data were published.

The author has the gift of a lucid writing style and, as a practicing statistician at the University of Chicago, is fully conversant with the subject whose history he chronicles. He restates important results in modern notation so today's reader can follow key derivations. The mathematical level of the text has been kept as simple as possible, given the nature of the subject. (It is surprising how much statistics one can really understand given only a reasonable command of algebra.) There are two stylistic complaints I must lodge, however. First, the author has a disconcerting habit of stressing again and again that some mathematician's insights were not, perhaps, up to the modern standard of clarity and rigor but were good approximations given the mathematician's background. I hardly think it necessary to apologize for lacunae in the works of men such as Gauss, De Moivre, and Laplace. Second, the author has a fondness for puns that are really execrable. "Simpson's early livelihood was earned as a weaver, but a different future loomed ahead" (p. 88), and "the derivation he gave was . . . suggested by his colleague Professor A.F. Moebius (who was clearly a many-sided talent)" (p. 247) are two examples. However, these are quite minor irritants in a book that fascinated me. I think that anyone with an interest in the history of science and a modicum of mathematical skill will wish to read this book.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

An Unusual Presentation of Vitamin B_{12} Deficiency

SIR: Organic psychosis due to vitamin B_{12} deficiency has been described previously (1–4). We recently treated a patient who had a paranoid psychosis without any change in cognition that was fully reversible with vitamin B_{12} supplementation alone.

Ms. A, an 89-year-old white woman, was admitted to a long-term care facility following hospitalization for treatment of a skin ulcer. She had been independent in all areas of daily living until 9 months before her hospitalization, when she developed the belief that her son-in-law was preventing her from being with her family. She began withdrawing and became confined to her home. She had no history of previous psychiatric disturbance. Results of in-hospital blood counts and chemical analyses were normal. She began to mistrust the hospital staff and refused to return home with her daughter. Her medical history showed only peripheral vascular disease. At the long-term care facility, her only medication was multivitamins. After 2 months, she began to withdraw from activities, stating that others were talking about her and that the staff did not like her. A psychiatric examination at that point revealed a somewhat agitated but oriented woman. Her speech was rapid and coherent, with some tangentiality. She had paranoid ideas but no thought flooding, feelings of grandeur, or hallucinations. Her mood was mildly elevated with an appropriate affect. A cognitive examination revealed no gross deficits, and her score on the Mini-Mental State examination was 26 out of 30. She was given a diagnosis of delusional disorder or affective disorder, manic type, with psychosis of uncertain etiology. She refused all further workup and treatment.

Over the following 12 months, the paranoia persisted without medical problems until Ms. A developed severe vomiting, diaphoresis, and shortness of breath. Blood analyses revealed a hemoglobin level of 6.5 g/dl and a hematocrit of 18.9%; her serum lactate dehydrogenase level was 1960 U/liter. An ECG showed an acute anterior wall myocardial infarction. Ms. A was treated and eventually recovered from the acute infarction. Evaluation of her anemia revealed normal serum folate and iron levels. Her serum vitamin B_{12} level was 47 pg/ml (normal=220–799 pg/ml), and the peripheral smear showed macrocytosis with hypersegmented neutrophils. The results of a neurological examination were unremarkable, including normal vibratory and position sensation. On a repeat Mini-Mental State examination, Ms. A again had a score of 26. Vitamin B_{12} replacement therapy was begun with hydroxocobalamin, 1000 μg/day i.m. for 3 days, which was followed by weekly injections for 3 weeks, then an injection once every month. Within 4–5 days of starting the vitamin B_{12} replacement therapy, Ms. A asked to eat in the dining room with everyone else. Her paranoia and anemia resolved, and she resumed full participation in daily activities at the long-term care facility. At 6-month follow-up, she showed no deterioration in mental function.

The literature indicates that psychiatric syndromes due to vitamin B_{12} deficiency can develop with or without anemia (1–4). Vitamin B_{12} deficiency left uncorrected can progress to dementia and cerebral and spinal cord lesions. It has become standard practice to evaluate serum B_{12} levels in individuals who present with new-onset dementia (5). This case reemphasizes the need to assess serum B_{12} levels in elderly patients with new onset of organic psychosis in the absence of dementia.

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Adverse Reaction to Use of Caffeine in ECT

SIR: We would like to report an adverse cardiovascular response to the use of caffeine to lengthen seizures in ECT.

Mr. A, a 49-year-old white man, was admitted to the hospital with a diagnosis of major depression, recurrent, with mood-congruent psychotic features. He was treated with a total of 12 ECTs, and there was marked improvement in his depression and resolution of the psychosis. However, the length of the seizures progressively decreased, as the treatments continued, to a subtherapeutic duration of 20–24 seconds, despite use of the highest settings on the ECT machine. Before treatment 12, intravenous caffeine was administered in hopes of lengthening the seizure. On the morning of this final ECT, the patient received 0.2 mg of glycopyrrolate 1 hour before the treatment. In addition, he continued to receive the metoprolol, 50 mg b.i.d. by mouth for hypertension, which he had been taking throughout the entire course of the ECTs. Upon arrival at the treatment room, Mr. A received 500 mg of caffeine sodium benzoate intravenously over approximately 90 seconds. During the course of the caffeine administration, there were no significant changes in his blood pressure or pulse. Immediately after the administration of caffeine, 60 mg of methohexital were given intravenously, during which time there was a rapid rise in his pulse from approximately 75 beats/minute to the 150–170 range, as well as an increase in his diastolic blood pressure from 75 to 110 mm Hg. The patient remained hypertensive and tachycardic as 60 mg of succinylcholine were administered and the shock treatment was given. Interestingly, there was no increase in blood pressure or pulse during the seizure, which was of 72 seconds' duration. After the seizure, Mr. A's blood pressure and pulse rapidly returned to normal levels. There was considerable postictal confusion, but this was attributed to the marked increase in the length of the seizure.

We found the use of intravenous caffeine very effective in increasing the length of seizure during ECT, as others have found (1). However, hypertension and tachycardia appeared to be side effects; these had not been present in the preceding caffeine-free treatments.

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Failure of Sleep Deprivation to Prolong Seizures in ECT

SIR: Two articles in the September 1987 issue of the *Journal* (1, 2) described the use of caffeine to lengthen seizures in ECT. We wish to report a case in which a nonpharmacologic intervention, sleep deprivation, was used in an attempt to achieve the same effect.

Mr. A was a 65-year-old man who had severe psychotic depression complicated by panic attacks with marked hypertension. Evaluation of the patient for pheochromocytoma produced negative findings. Results of thyroid studies were normal. ECT was initiated, with a Medcraft B24-III device and bilateral electrode placements. The length of the seizures was monitored by the blood pressure cuff technique. At the first treatment, a stimulus of 140 V for 0.6 second failed to elicit a seizure. The patient was restimulated at a setting of 140 V for 1.0 second after hyperventilation. No seizure was elicited. A final attempt with two stimuli of 140 V for 1.0 second elicited a seizure lasting 36 seconds. At the second treatment session, two stimuli of 140 V for 1.0 second produced a seizure lasting only 20 seconds. At the third session, an increase to two stimuli of 150 V for 1.0 second produced a 16-second seizure. At the fourth treatment, two stimuli at the maximum setting (170 V for 1.0 second) produced a 25-second seizure.

The patient was improving, but our concern that the short seizures were possibly decreasing the effectiveness of the ECT prompted us to consider giving caffeine. However, because caffeine was not immediately available and because of the patient's hypertension, we chose instead to try sleep deprivation before the next treatment. We hoped that sleep deprivation might lower the seizure threshold and/or produce a longer seizure. Also, we wondered whether the effects of ECT and sleep deprivation might be additive.

The night before the next treatment, Mr. A slept for 30 minutes, from midnight to 12:30 a.m. He appeared less depressed before his treatment at 7:30 a.m. Again, two stimuli at the maximum setting of 170 V for 1.0 second were given, and he was hyperventilated. The seizure lasted 20 seconds, suggesting that sleep deprivation did not have the desired effect of increasing seizure length. Thirty minutes after this treatment, and before going to sleep, Mr. A was markedly improved and more cheerful than he had been at any time previously. Later that day he remained moderately improved. Sleep deprivation was repeated before the sixth treatment: the patient was kept awake the entire night. The maximum setting with two stimuli produced a seizure lasting 22 seconds.

Our trial in one patient failed to demonstrate an augmenting effect of sleep deprivation on length of seizure. Sleep deprivation is routinely used in EEG laboratories to elicit epileptiform activity. It is believed that sleep deprivation has intrinsic activating effects and does not work merely by ensuring that the subject sleeps during the recording (3). We had hoped that such an activation might result in a longer seizure during ECT.

Sleep deprivation is also well-known as an effective but transient antidepressant treatment. It clearly had a beneficial effect on our patient. Whether this effect was independent of ECT or interacted with the effects of ECT is unknown.

Although our trial in one patient was unsuccessful, it may be worthwhile to continue to investigate the possibility that sleep deprivation, used in conjunction with ECT, has beneficial effects on clinical outcome.

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Glutethimide Intoxication and Withdrawal

SIR: Glutethimide abuse is again on the rise. Once popular as a sedative-hypnotic, glutethimide is now used orally in a combination with codeine (known as a "load") for its euphoriant properties, which are subjectively similar to those of parenteral opiates (1). We describe a case of glutethimide withdrawal devoid of the classic sedative abstinence signs of hypertension, tachycardia, and agitation (2) and suggest that the clinical picture commonly ascribed to glutethimide overdose may in reality be due to a hidden abstinence syndrome.

Mr. A, a 35-year-old white man with a longstanding daily intake of 6 g of glutethimide and 2 g of codeine, was brought in a comatose condition to a Veterans' Administration hospital. His systolic blood pressure was 100 mm Hg, his pulse was 126 beats/minute, and his temperature was 101°F. Results of a cardiorespiratory examination were unremarkable. His pupils measured 3 mm and were reactive. He withdrew all extremities in response to pain and demonstrated normal deep tendon reflexes. The remainder of the neurological examination revealed no focal signs. Mr. A was intubated for airway protection. Serum studies revealed a glutethimide level of 3.3 μg/ml (therapeutic range=2–12 μg/ml), a mixed acidosis, and leukocytosis; a urine toxicology screen identified glutethimide and codeine. After Mr. A had been given thiamine, naloxone, sodium bicarbonate, and hydration, his blood pressure stabilized at 120/66 mm Hg and he became arousable.

On day 2 in the intensive care unit, Mr. A became oriented and was extubated. His vital signs, acid-base status, and WBC were now normal. He had apparently recovered from what was considered to be either a purposeful or an accidental overdose. However, on day 3 he became increasingly lethargic, and on day 4 he suffered a generalized tonic-clonic seizure; he was given phenytoin, 1 g. At this point, given his stable vital signs and lack of tremulousness, we considered focal intracranial pathology and surreptitious reintoxication, rather than withdrawal from the sedative, as possible causes. Lumbar puncture, CAT scan, and EEG results did not point to a diagnosis, and repeat toxicology screens produced negative results.

There was no change in Mr. A's vital signs on days 3–8; his mental status fluctuated from lethargy to total unresponsiveness. Neurological examination during this period revealed only myoclonic jerking of the fingers.

Atypical abstinence syndrome was considered as a diagnosis by exclusion, and on day 8 phenobarbital, 60 mg every 3 hours, was begun. Within 24 hours Mr. A began to have purposeful movements and intelligible speech. Over the next 4 days he regained normal mental status; he was transferred to the drug detoxification unit.

The patient's initial obtunded sensibility appeared consistent with severe intoxication (3). However, despite the normalization of vital signs and initial metabolic abnormalities, his mental status subsequently worsened. The seizure and myoclonic jerking during this period of improving vital signs were, in retrospect, the only signs of glutethimide abstinence (2, 4).

Such prolonged periods of blunted sensibility have in the past been ascribed to glutethimide intoxication, which has been thought to follow a waxing and waning course that continues for up to 5 days (3). This variability has been ascribed to toxic metabolites, drug lipid solubility, enterohepatic circulation, and delayed gastric emptying (5). However, this case suggests that such a clinical picture may not be due to intoxication but rather to an abstinence syndrome devoid of classical sedative withdrawal signs and symptoms (2).

To treat apparent glutethimide intoxication with an additional sedative involves substantial risk. However, untreated sedative withdrawal carries an ominous prognosis (2). We suggest that an extended period of obtunded sensibility accompanied by subtoxic glutethimide levels may be due to glutethimide abstinence rather than intoxication or one of its complications.

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Sexual Dysfunction Related to Alprazolam Treatment of Social Phobia

SIR: We would like to report the development of reversible sexual dysfunction in two patients being treated with alprazolam for social phobia. Both patients had been randomly assigned to treatment with alprazolam (up to 4.9 mg/day), phenelzine (up to 90 mg/day), or placebo in a double-blind fashion. In each case, before the blind condition was broken, the sexual dysfunction led the treating psychiatrist to believe that the patient was receiving phenelzine.

Case 1. Ms. A, a 47-year-old married white woman, sought treatment for extreme fear and avoidance of public speaking (i.e., fear of talking in the presence of groups). She would tremble and felt that everyone in the audience was aware of her anxiety and would ridicule her. She met the *DSM-III* criteria for social phobia and had no concurrent depressive symptoms. Before beginning treatment, Ms. A described herself as a sensuous, warm person who usually had orgasms. During the 4th week of treatment, while she was taking 4.2 mg/day of alprazolam in divided doses, she noted decreased libido and decreased sexual thoughts. Three weeks later, while still taking the same dose of medication, she became anorgasmic. The anorgasmia and decreased interest in sex continued until her dose of alprazolam was tapered and then discontinued. At a dose of 1.4 mg/day, her interest in sex and her ability to achieve orgasm returned, and at a 2-month drug-free follow-up, her sexual functioning had returned to her normal baseline. Her social phobia improved from severe impairment to mild impairment during her treatment. There was no recurrence of symptoms at follow-up.

Case 2. Mr. B, a 32-year-old married white man, sought treatment for anxiety in formal social situations. He had panic attacks when called upon to give presentations in class, and he felt that his anxiety symptoms impaired his job performance. During the 6th week of treatment, while he was taking 4.2 mg/day of alprazolam in four divided doses, Mr. B noted decreased erectile capacity and difficulty reaching orgasm. The following week, while still taking the same dose, he noted inability to ejaculate. Despite this sexual dysfunction, he had shown a marked improvement in his social phobia symptoms, with a decrease in his global ratings from 5 (severe impairment) to 1 (no symptoms), and he agreed to increase his dose of alprazolam to 4.9 mg/day. At this higher dose there was no change in his sexual functioning. During week 9, erectile function returned, but the inability to ejaculate persisted. By the 11th week, Mr. B was able to ejaculate, but ejaculation was delayed. When his dose of medication was tapered, his sexual function returned to his usual baseline, and his social phobic symptoms recurred, but to a lesser degree.

Sexual side effects of alprazolam have been previously reported (1–3) during open treatment with doses ranging from 3 to 10 mg/day. As in previously reported cases (1, 2), sexual functioning in our patients returned to baseline when the dose of alprazolam was reduced. In the questionnaire survey reported by Lydiard et al. (3), almost half of the 32 patients showed impaired sexual functioning while taking alprazolam. However, three of the 32 patients noted improved orgasmic functioning, and another four reported increased libido.

While it could be argued that sexual dysfunction in anxiety disorder patients is related to the anxiety rather than the medication, the marked improvement in our patients' social anxiety symptoms during treatment and the return to baseline of sexual functioning when the medication was decreased appear to implicate the medication.

These cases have led us to inquire more systematically about changes in sexual functioning during blind treatment trials, and a future report will present the relative prevalence of this problem in patients treated with alprazolam and phenelzine. Considered together with the previous reports (1–3), our preliminary findings suggest that sexual dysfunction may not be an uncommon side effect of alprazolam pharmacotherapy.

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Panic Attacks and Exposure to Chemical Agents

SIR: Stephen R. Dager, M.D., and associates (1) described three cases of exposure to solvents that resulted in symptoms characteristic of panic disorder. Two of these patients also had a positive response to sodium lactate infusions. The solvents implicated in that report were methyl ethyl ketone and toluene (patients 1 and 3) and alkylaryl polyether alcohol, organic phosphate ester, and iso-octyl phosphate acid (patient 2). We report another case of panic attacks after exposure to a chemical agent.

> Mr. A, a 33-year-old white aircraft mechanic developed panic disorder after he accidentally inhaled fumes of "superglue" containing cyanoacrylate. (This same chemical is present in the superglue available for household use.) The patient had no previous history of panic attacks. He reported feeling dizzy and tremulous for a period of 24 hours after the exposure. He was seen by several physicians who were unable to find any abnormalities upon neurological and cardiological evaluation. The findings of his routine laboratory tests, ECG, and stress tests were unremarkable. The patient had a mitral valve prolapse syndrome that had been diagnosed several years earlier.
>
> A few days after Mr. A was exposed to superglue, he developed episodes of intense anxiety, feelings of fright and losing control, fear of dying, dizziness, heart pounding, chest discomfort, sweating, shakiness, and severe exhaustion. These attacks would last a few minutes to an hour, but he felt exhausted for several hours after some of them. The attacks were usually precipitated by physical exercise, so Mr. A had to decrease his physical activity. He reported the frequency of the attacks as one per week, but he did not want any treatment because he felt that they did not significantly interfere with his occupational or social life. He reported a decrease in the severity and frequency of the attacks at follow-up 6 months after the initial evaluation.

This report, together with that of Dr. Dager and associates, suggests that chemical agents may precipitate panic disorder in predisposed individuals. This case also suggests that panic disorder patients should avoid exposure to superglue.

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Dr. Dager and Associates Reply

SIR: Dr. Yeragani and colleagues' description of a case of panic disorder temporally related to superglue exposure offers further support of our observation that panic disorder can occur as an idiosyncratic, non-dose-related response to chemical exposure. Their letter suggests a reaction to cyanoacrylate, which is not an organic solvent but a potent mucous membrane irritant. Superglue also contains organic solvents, which may have precipitated their patient's panic attacks, as suggested by our article.

However, our recent experience suggests that chemicals other than organic solvents may also be associated with panic. Since our initial observations, we have evaluated patients who developed panic attacks following exposure to ammonia from a diazo printer, ozone from a photocopier, chlorine from a pulp mill factory, and nitrous oxides produced from welding. These chemicals are primarily polar molecules, which do not easily cross membranes and, like cyanoacrylate, have primarily local irritant effects on the upper and lower respiratory tract and conjunctiva. Unlike organic solvents, which are lipophilic and cross membranes readily, these substances probably do not have direct CNS effects (1). Thus, direct CNS toxicity may not be necessary for the precipitation of panic.

We cannot concur with the recommendation by Dr. Yeragani and associates that patients with panic disorder avoid superglue. There are as yet no data suggesting that chemical exposure can exacerbate preexisting panic disorder.

Both the prevalence of and individual risk factors for developing panic in response to a particular class of chemicals are unknown, pending prospective studies. Finally, it would be impractical to steer patients away from all possible chemical exposures. Recommending avoidance of anything to patients at risk for the development of pathological avoidant behavior may cause further problems and should be done only if the association is clear-cut and incontrovertible.

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Amantadine for Treatment of Cocaine Dependence in Methadone-Maintained Patients

Sir: We report here the results of a 6-week open trial of amantadine for the treatment of cocaine dependence in 12 methadone-maintained patients.

Known cocaine-using, methadone-maintained patients were referred for amantadine treatment by clinic staff and evaluated by means of a psychiatric interview, physical examination, and laboratory studies (SMA-20, CBC, urine toxicology screen, and urinalysis). Medically healthy male and infertile female patients, ages 21–50 years, were included if they met *DSM-III* criteria for cocaine abuse for more than 3 months and were free of schizophrenia, bipolar disorder, attention deficit disorder, residual type, epilepsy, and/or concurrent nonopioid substance dependence disorders. The dose of amantadine HCl was 200 mg/day p.o. for 3 weeks, followed by an optional increase to 200 mg b.i.d. for 3 subsequent weeks. Monday through Friday the patients' ingestion of the 200 mg of amantadine was observed by the staff. Methadone dosage was constant throughout the study. Informed consent was obtained 1 week before treatment began.

The level of cocaine craving was assessed weekly by self-report; the score was computed as the sum of four 10-point items (range=0–36). Cocaine use was also assessed weekly by self-report (the score was computed as the product of the number of days of cocaine use times the maximum daily expenditure for cocaine) and by twice-weekly urine toxicology screens (thin layer chromatography with EMIT confirmation). The Beck Depression Inventory (1) was administered weekly, beginning 1 week before amantadine treatment, to measure depressive symptoms.

Twelve of the 18 initial participants completed 6 weeks of treatment; all 12 of them chose to increase their amantadine dose to 200 mg b.i.d. after the third week. The 12 patients (11 male, one female) had a mean age of 33 years (range=23–40 years). Seven were Hispanic and five were black. The mean duration of their *DSM-III*-defined cocaine abuse was 4.6 years (range=1–23 years). The route of cocaine administration was intranasal for three subjects, freebase for two, intravenous for two, and mixed for five.

Significant decreases between pretreatment cocaine craving level, cocaine use self-report, and Beck depression score and the respective averaged results for the fifth and sixth weeks (late treatment) were noted (Wilcoxon matched-pairs, signed-ranks test, two-tailed): mean±SD cocaine craving score=24 ± 5 versus 11 ± 9; $Z=2.98$, $p<0.01$; mean±SD cocaine use score=714 ± 603 versus 161 ± 238; $Z=2.98$, $p<0.01$; mean±SD Beck depression score=13±[illegible] versus 6 ± 7; $Z=2.51$, $p<0.02$. The sum of the six weekly cocaine use reports was correlated with the number of cocaine-positive urine samples (Spearman $r=0.77$, $p<0.02$), supporting the validity of the cocaine use reports.

The only side effects of amantadine treatment were reported by two study dropouts. One patient reported a mild headache with dizziness, and another reported an increase in cocaine craving after the first dose of amantadine.

These results in conjunction with those in other reports (2) warrant further controlled studies to determine whether amantadine is efficacious in reducing cocaine craving and use in cocaine-dependent patients.

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Thyroid Disease and Dementia of the Alzheimer Type

Sir: A higher frequency of thyroid disease in the female relatives of subjects with Down's syndrome has been reported (1). This finding has led to a number of studies examining the possible relationship between previous thyroid disease and dementia of the Alzheimer type, since it is known that there is a strong relationship between trisomy 21 and the neuropathology of dementia of the Alzheimer type. The results to date have been inconclusive. In an earlier study (2), Heyman et al. found a greater frequency of previous thyroid disease in female patients with Alzheimer's disease than in a community population. In a more recent case-control study (3), the same group found a higher frequency of previous thyroid disease in female patients with Alzheimer's disease than in female control subjects. However, two other studies (4, 5) failed to replicate Heyman et al.'s findings.

In an attempt to examine this issue in our own population of Alzheimer patients, we carried out a retrospective analysis of the medical records of 50 of our patients (20 male and 30 female) who met strict *DSM-III* inclusion criteria for primary degenerative dementia and 25 age-matched control subjects (11 male and 14 female) recruited from a pool of elderly volunteers and biologically unrelated relatives of Alzheimer's disease probands. Only a history of goiter, thyroid surgery, thyroid irradiation, or definite hypo- or hyperthyroidism was considered positive evidence of thyroid disease in both the patients and the control subjects. Basal levels of thyrotropin-stimulating hormone (TSH) of 36 of the patients and 11 of the control subjects were known.

There were no significant differences between the two study groups in terms of age, sex, and basal TSH level. Sixteen percent of the female Alzheimer patients and 10% of the male Alzheimer patients had a history of previous thyroid disease, compared to 14% of the female control subjects and 8% of the male control subjects (nonsignificant difference, by Fisher's exact test).

The results of this retrospective study of our Alzheimer patients do not support the hypothesis that previous thyroid disease is a risk factor for dementia of the Alzheimer type. However, larger prospective studies will be necessary to determine the true relationship, if any, between abnormal thyroid function and dementia.

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Lithium and Antithyroid Antibodies

Sir: Lithium can cause both subclinical and overt hypothyroidism, involving in some instances an autoimmune mechanism (1, 2). We made a study of 60 psychiatric patients (37 women, with a mean±SD age of 53±12.4 years, and 23 men, age 55±12.4 years)—the majority (N=40) of whom were suffering from major affective disorders (manic-depressive psychosis)—treated with lithium for at least 6 months (mean±SD length of treatment=69.5±41.5 months). The mean±SD lithium blood level during this time was 0.65±0.2 meq/liter. The patients were monitored clinically and biologically for thyroid function (T_3, T_4, and thyrotropin-stimulating hormone [TSH] levels) over a 1-year period. Their levels of thyroid antibodies (microsomal and thyroglobulin) were also determined. Eighty percent of the female and 95% of the male patients had been administered or were receiving long-term psychotropic medication (neuroleptics or antidepressants) along with the lithium, but we do not think that this greatly affected our findings.

At the beginning of the study, 16 (27%) of the patients (13 female and three male) had laboratory values indicative of hypothyroidism; four of the female patients showed slight clinical symptoms. Of these patients, 12 required L-thyroxine. Of the 60 patients, 20% (11 female and one male) already had thyroid antibodies. Among the female patients with hypothyroidism, six had thyroid antibodies; no male patient had any. The sample of 60 patients could be divided into the group receiving and the group not receiving L-thyroxine (L+ or L−) and into the group with and the group without thyroid antibodies (TA+ or TA−), giving four groups: L−TA− (N=43), L−TA+ (N=6), L+TA− (N=5), and L+TA+ (N=6).

During the study, no significant difference was found in TSH level between the L−TA− and the L−TA+ groups. Within the L−TA+ group, no significant variation in TSH level occurred. Within the L−TA− group, TSH levels decreased; 10 patients dropping out accounted for this. In both of these groups, the T_3 levels remained within normal limits during the study. T_4 levels were within normal limits, except for two patients in the L−TA− group who had higher levels at the beginning of the study.

Thus, at the beginning of the study, thyroid antibodies had been detected in 12 patients (11 female and one male). At the 6-month evaluation, another male patient had developed antibodies. Among these 13 patients, seven were euthyroid, whereas six (46%) who needed L-thyroxine had the highest levels of microsomal antibodies. In eight of the 13 patients with thyroid antibodies, thyroglobulin antibodies were detected. Two of the seven euthyroid patients showed thyroglobulin antibodies, and all six of the hypothyroid patients had thyroglobulin antibodies. No significant difference was found between duration of lithium treatment and presence of thyroid antibodies. An increase in thyroid antibody levels was observed in five patients who were receiving L-thyroxine (one had only microsomal antibodies and four had microsomal and thyroglobulin antibodies) and in four patients who had not been given L-thyroxine.

The prevalence of thyroid antibodies in this group of 60 patients was 21.7%, whereas in the general population it is estimated to be about 10% (3). All of the patients who had thyroglobulin antibodies also had microsomal antibodies, but the opposite was not true. These results are not in agreement with a previous report on this subject (1), and a more recent prospective study (2) measured only thyroid microsomal antibodies.

Our results may reflect three possible modes of action of lithium on the thyroid gland: through the autoimmune system, through cAMP, or both.

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The Organic Mental Disorders Subsection of *DSM-III-R*

Sir: Several aspects of the organic mental disorders subsection of *DSM-III-R* need to be highlighted and reviewed for possible inclusion in *DSM-IV*. I note that *DSM-III-R* does not have a specific diagnostic category for alcoholic mood disorder. The only psychoactive substance-induced organic mental mood disorders are included under hallucinogen- and phencyclidine-induced disorders. As both a psychiatrist and a specialist in addictions, I have found in my clinical experience that there is an intricate relationship between alcoholism and depression, including alcoholism and concomitant affective disorder (1) and alcohol-induced organic mood disorder. Previous studies have indicated that chronic alcohol ingestion causes depression (2–4) and that simple withdrawal states have a prominent affective component (5).

In addition, *DSM-III-R* does not include organic anxiety disorders induced by sedatives, hypnotics, and minor tranquilizers. These disorders are very commonly found in clinical practice.

In any case, my question is both pragmatic and theoretical. If one comes across an alcohol-induced organic mood disorder, how is it to be classified according to *DSM-III-R*? Should it be classified as 1) an organic mood syndrome, probably alcohol induced, or 2) an axis I organic mood disorder secondary to alcoholism? In my mind, the confusion arises because there is no separate category of alcoholic mood disorder in *DSM-III-R*. A similar question may also be raised with respect to sedative-, hypnotic-, and anxiolytic-induced organic mood syndrome and organic anxiety syndrome. I understand that if a patient has both alcoholism and an affective disorder, these are listed as two separate diagnoses on axis I.

A major source of confusion in this subsection of *DSM-III-R* is the differential conceptualization of the diagnosis of organic mental syndromes and organic mental disorders. Both categories assume organic etiology. The differentiating factor is the degree of certainty about the proposed cause. The optimal approach may be to eliminate the category of organic mental syndromes. Then axis I would specify the presenting organic mental disorder. Additional axis I and/or axis III diagnoses would indicate the disorder causing the organic mental disorder. The degree of etiologic correlation would be specified on a continuum as definitely, probably, or possibly causative. This would give clinicians and researchers the opportunity to determine for each patient the strength of the correlation between the organic mental disorder and the etiogenic disorder in view of the clinical, laboratory, historical, or other evidence.

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Adrenal Weight and Violent Suicide

SIR: The article by Katerina Dorovini-Zis, M.D., and Athanasios P. Zis, M.D., "Increased Adrenal Weight in Victims of Violent Suicide" (1), was both interesting and provocative. However, their finding of increased adrenal weight in 16 victims of violent suicide requires clarification.

It is unclear whether depressed patients in general have adrenal hyperplasia as a consequence of enhanced cortisol secretion, and further, whether unipolar and bipolar patients and delusional and nondelusional depressed patients differ in adrenal weight. Also, a larger number of subjects should be studied, including medical-surgical patients and normal subjects as well as alcoholics and others whose dexamethasone suppression test results and cortisol levels have previously been studied (2, 3). Finally, a CAT scan of the abdomen could well be used to study these questions. If exposure to radiation is a concern, an alternative means would be nuclear magnetic resonance scans.

I was intrigued by this study but feel that it was premature to conclude that there is a correlation between adrenal size and violent suicide, or for that matter, adrenal size and attempted suicide.

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SIR: Drs. Dorovini-Zis and Zis suggested that the observed increase in the adrenal weight of suicide victims is due to chronic hyperstimulation by ACTH during the course of depression. I would like to present evidence from the literature which suggests that ACTH plays only a permissive role in adrenal growth and that a pro-γ-melanocyte-stimulating hormone (MSH) peptide derived from the N-terminal portion of the proopiomelanocortin precursor protein is responsible for adrenal growth.

Pro-γ-MSH is concomitantly secreted with ACTH and β-endorphin from pituitary corticotrophs (1). Lowry et al. (2) demonstrated in rats that adrenal growth and proliferation involve postsecretional proteolytic cleavage of pro-γ-MSH at the adrenal gland. Furthermore, Rao et al. (3) showed that administration of ACTH antiserum to unilaterally adrenalectomized rats did not prevent an increase in weight of the remaining adrenal gland. Al-Dujaili et al. (4) demonstrated significantly higher corticosterone by $ACTH_{1-24}$ and γ-MSH precursor infusion than with $ACTH_{1-24}$ alone. Interestingly, pro-γ-MSH peptides may be secreted from melanotrophs of the pars intermedia independently of ACTH secretion from anterior pituitary corticotrophs (2).

Pro-γ-MSH peptides secreted by corticotroph or melanotroph cells of the pituitary may be responsible for the observed increase in adrenal weight of suicide victims.

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Drs. Dorovini-Zis and Zis Reply

SIR: As we clearly indicated in our report, our findings regarding a relationship between increased adrenal weight and violent suicide were preliminary; thus, Dr. Solomon's expression of interest with skepticism is well taken. As we specifically stated, we did not conduct a post-mortem psychiatric investigation, and we considered the data in the coroner's file incomplete. Therefore, any statements about an association between adrenal size and depression must be based on the well-known relationship between depression and suicide and be considered tentative at this point.

For the same reason, we cannot address any of the questions raised by Dr. Solomon regarding the relationship between depression subtype and adrenal weight. We are somewhat at a loss about how one would follow his suggestion and design a study in which cortisol levels and DST results would be monitored before suicide or accidental death. We refer him, however, to a recent report by Amsterdam et al. (1), who found an association between depression and increased adrenal size as estimated by computed tomography. The DST was administered to the patients in that study. We take exception to Dr. Solomon's suggestion that "medical-surgical" patients should be included as control subjects in studies of adrenal gland size in depression; the adrenal cortex of these patients may be enlarged because of the stress associated with the presence of a chronic or debilitating and protracted disease.

We did not intend to convey the impression that we believe that the observed increase in adrenal weight in suicide victims is necessarily or exclusively the direct result of chronic hyperstimulation by ACTH. We agree with Dr. Dominy that other factors may play a role. In fact, not only pituitary factors, as he suggests, but also extrapituitary factors may be responsible, at least in part, for an increase in adrenal gland size during the course of depression. There is a growing body of evidence that neural activity can directly affect endocrine organs classically considered to be entirely controlled by hormonal feedback mechanisms (2). Of particular relevance here is evidence that the autonomic nervous system may mediate cell proliferation (compensatory adrenal growth) in the adrenal cortex of experimental animals (3, 4).

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Immunocompetence During Stress

SIR: Alteration in immunocompetence during stress relates to basic concepts of homeostasis and adaptation. These basic concepts need clarification to interpret the data presented by Joseph R. Calabrese, M.D., and associates in their article on alterations in immunocompetence during stress, bereavement, and depression (1).

Walter B. Cannon (2) discovered that the awareness of a threat triggered an intense activation of the sympathetic nervous system; he called the results of this acute activation the "fight-or-flight" reaction. Dr. Calabrese and colleagues mentioned that lymphocytes in the spleen are surrounded by noradrenergic fibers, but Cannon did not find changes in the immune tissues during the fight-or-flight response. We cannot ignore the fact that the awareness of a threat also triggers a behavioral response which eliminates the threat before immunologic changes can take place. When the mental arousal is not a threat, the behavioral response does not occur immediately; nevertheless, the sympathetic nervous system is still activated to some degree. Under those conditions, noradrenergic fibers in the spleen, and probably in other areas, are active for an extended period of time, and immunologic changes have time to develop.

In the 1930s Hans Selye (3) discovered another response to stressors—in this case triggered by a somatic condition, tissue damage. This response resulted in various changes within the body that Selye called "general adaptation syndrome," including an involution of thymicolymphatic tissues. Selye considered the symptoms to be an alarm reaction alerting the organism to a disturbance that could spread to other parts of the body. Consequently, the organism produces another biologic response to restore the homeostasis and prevent further changes. While the body is repairing tissue damage, the two responses counterbalance each other and no symptoms are noted. Selye called that condition "stress" (4). The following conclusions result from the discoveries I have just mentioned.

1. The fight-or-flight reaction discovered by Cannon is not stress but occurs during the mental stress accompanying any state of awareness. It does not include immunologic changes because the awareness of a threat is promptly terminated by a behavioral response.
2. If a state of awareness is not terminated, the organism suffers from a persistent mental stress that keeps the sympathetic nervous system constantly active. Under these conditions, the immune system suffers changes that can be detected.
3. The alarm reaction discovered by Selye includes immunomodulation but is not stress.
4. When the alarm reaction is counterbalanced by another adaptive response, the symptoms of the general adaptation syndrome disappear, but the physiological functions of the body are under stress.

These statements concerning stress relate only to the original works of Cannon and Selye. We now have evidence that the body produces other biological mechanisms that must be considered part of the stress response.

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Dr. Calabrese Replies

SIR: I agree with Dr. Fernandez that it is important to consider the concepts of homeostasis and adaptation when discussing data which suggest that stress, bereavement, and depression can alter immunocompetence. It was, however, the nineteenth-century physiologist Claude Bernard who first recognized the importance of homeostasis and adaptation and stated, "The constancy of the 'milieu interieur' is the condition of a free and independent existence" (1). Later, the pioneering work of Cannon and Selye greatly advanced awareness of the role that emotion plays in homeostasis and adaptation. Cannon provided observations that he believed important to his "emergency theory of emotion" and in 1915 coined the term "fight-or-flight" response. He argued that whereas the parasympathetic branch of the autonomic nervous system regulates such vegetative functions as digestion, the sympathetic branch prepares the body for defense against stress.

On the other hand, the work of Selye greatly clarified the coordinated roles of the autonomic nervous system, endocrine system, and immune system in the response to stress. He suggested that there are three distinct stages in the body's response to stress. The first stage is accompanied by activation of both the hypothalamic-pituitary-adrenal-cortical and the sympathoadrenal medullary axes and is called the "alarm reaction." The second is the "stage of resistance," during which the most appropriate local defense against stress is organized. The third stage occurs if the stress is too strong or too prolonged. In this "stage of exhaustion," the body's resistance declines and death usually follows.

Dr. Fernandez concludes that the fight-or-flight response does not involve immunologic changes because behavioral responses terminate the threat. Frequently, however, a behavioral response is unsuccessful in its attempt to accomplish this, and the organism sustains trauma. There is reason to believe that neuroendocrine changes accompanying the alarm reaction have immediate adaptive immunomodulating properties which prepare the organism for the possibility of this incoming trauma. In fact, it is clear that the glucocorticoids and catecholamines have potent immunomodulating properties that are frequently seen within minutes.

It is true that chronic arousal leads to persistent activation of the sympathetic nervous system and that immunologic changes typically occur as a result of this activation. I disagree, however, with the suggestion that the alarm reaction is not a stress. Selye himself addressed this issue by noting that the body's attempts to deal with stress can themselves be stressful to the body, resulting in what he called "diseases of adaptation." For example, high levels of ACTH and corticosteroids in the body can lead to ulceration, cardiac disease, and high blood pressure.

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Suicide Attempts by High School Students

SIR: Almost 9% of 380 academically select New York high school students had attempted suicide, according to an article by Jill M. Harkavy Friedman, Ph.D., and associates (1) published in this journal. The authors stated that their results must be replicated in other high school samples.

We have completed and analyzed a study of 370 nonselected adolescents, ages 14–18 years (53% were boys), who are patients at a five-pediatrician private practice office. The survey instrument was a pencil-and-paper pilot test designed to discover adolescents who may have drug or alcohol abuse problems. Of the 360 patients who cooperated with the study, 19 (5.3%) noted that they had attempted suicide previously. There was no difference between the sexes in the numbers of suicide attempters in our survey. Preliminary analysis of the computerized data shows a strong association between abuse of drugs, including alcohol, and suicide attempts. It appears that 5%–9% of middle-class adolescents in metropolitan areas attempt suicide.

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Drs. Harkavy Friedman and Asnis Reply

SIR: With attention focusing recently on suicidal behavior among adolescents, it is becoming clearer that the frequency of suicide attempts is a problem of serious proportions. We are heartened that researchers across the nation are working to determine the magnitude of this problem. Drs. Schwartz and Wirtz found that about 5% of the 14–18-year-old patients of five private practice pediatricians reported suicide attempts. They did not find the differential sex ratio that we found in our study, however. They also identified a relationship between alcohol/drug abuse and suicide attempts.

In the next academic year after our survey, in a second sample of 279 students from the same school, we replicated our finding that 8.6% of students attending an academically select high school reported that they had tried to kill themselves. Drug and alcohol use was reported by both suicide attempters and nonattempters, although it was relatively more common among attempters. Our survey did not permit us to assess abuse of these substances. Recently, other researchers have also found that 7%–10% of adolescent students report suicide attempts (1, 2). Our finding that the female/male ratio of attempters was 3:1 has been replicated as well.

The discrepancies among these studies may reflect methodological differences more than actual differences in suicidal behavior. In our study and the studies of Smith and Crawford and of Josef et al., the subjects were attending school. Drs. Schwartz and Wirtz gathered their sample from pediatricians in private practice. It is possible that this medical sample was self-selected with regard to physical and mental health status and socioeconomic status, reducing the rate of suicidal behavior and altering the male/female ratio. Our samples were diverse with respect to these factors. In addition, it is unclear what question was posed to the adolescents in the study by Drs. Schwartz and Wirtz. We ask students, "Have you ever tried to kill yourself?" because in our pilot attempts to study suicidal behavior we found that adolescents often shied away from the word "suicide."

In our research we have found that specific suicidal behaviors, that is, thoughts, plans, and attempts, are related to psychosocial factors such as suicidal behavior of family members, depression, stress, impulsiveness, aggression, and premenstrual changes. For example, adolescents who reported persistent thoughts of killing themselves, accompanied by plans of how they might carry this out, were similar with respect to the psychosocial variables we measured to those who reported suicide attempts. Perhaps these adolescents represent a high-risk group. Therefore, we believe that it is imperative to ask about the entire spectrum of suicidal behaviors and not just suicide attempts.

We applaud Drs. Schwartz and Wirtz for attempting to expand our knowledge about the frequency of suicide attempts in the general adolescent population and its relation to other behaviors. We need a large-scale national study with standardized measures across samples before we can truly understand how widespread suicidal behavior is among adolescents. Further, we believe we have the potential to learn the most about treatment and prevention of suicidal behavior by studying the entire spectrum of suicidal behaviors.

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Action of Imipramine and Alprazolam in Panic Disorder

SIR: The data of Dennis S. Charney, M.D., and associates (1) on yohimbine-induced panic attacks certainly complement previous reports that support the relationship between panic anxiety and noradrenergic hyperactivity (2). It follows that this hyperactivity could remain unchecked because of a dysfunction of the α_2-adrenergic autoreceptor. I believe that Dr. Charney and associates' conceptual model of panic anxiety can be used to explain a finding of Aronson (3) in which 19 (37%) of his 51 panic disorder patients (including those with agoraphobia with panic attacks) experienced a stimulant reaction to imipramine.

Imipramine, like tricyclic antidepressants in general, has acute effects (within hours) on the blockade of the presynaptic uptake of amines. Activation of the α_2-adrenergic autoreceptor leads to reduced neuronal firing rates and reduced synthesis and turnover of norepinephrine. Continued imipramine-produced amine uptake blockade (over weeks) eventually leads to a decreased sensitivity of presynaptic α_2-adrenergic receptors, a return to normal of the neuronal firing rate and turnover of monoamines, and a decreased sensitivity of β_1-adrenergic receptors. α_1-Receptor upregulation also accompanies these changes over time (4).

Since most antidepressants cause acute as well as chronic uptake blockade of norepinephrine, does it not stand to reason that a substantial number of panic disorder patients (whose putative pathophysiology is noradrenergic hyperactivity unchecked by deficient α_2-autoreceptors) would have amphetaminelike reactions to acute doses of imipramine?

It is worth noting that of the 33 of Aronson's patients who could tolerate imipramine, the vast majority (88%, or 29) did exceptionally well in that they generally became panic free in 3–6 weeks. Since this time frame is strikingly similar to that usually associated with clinical improvement in depressed patients, one is tempted to speculate that the receptor changes which are generally assumed to parallel improvement in depressed patients may be involved in the improvement of panic disorder patients treated with antidepressants.

However, the effectiveness of alprazolam in panic disorder patients suggests that β_1 downregulation and α_1 upregulation are not necessarily requirements of an effective antipanic drug. In contrast to tricyclic antidepressants and monoamine oxidase inhibitors, alprazolam does not reduce the number of β-adrenergic receptors (5). Aronson also noted that, unlike tricyclic antidepressants or phenelzine, alprazolam did not cause amphetaminelike reactions. The effects of alprazolam may be explained by other data: although long-term treatment with alprazolam and with imipramine significantly reduces plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) baseline levels, only long-term alprazolam treatment is able to blunt yohimbine-induced increases in plasma MHPG and patients' ratings of anxiety/nervousness (6). Thus, the antipanic mechanism of action of alprazolam may be due in part to its effects on benzodiazepine-sensitive and noradrenergic neural systems, while the antipanic mechanism of action of imipramine may be due to its capacity to produce a variety of receptor adaptations. Recently, other benzodiazepines have been shown to have rapid antipanic activity at high doses. (D.S. Charney et al., "Efficacy of Lorazepam in Panic Disorders," paper presented at the 140th annual meeting of the APA, Chicago, May 9–14, 1987).

It would be intriguing to study the effects of yohimbine on Dr. Aronson's stimulant responders and imipramine on Dr. Charney and associates' yohimbine responders.

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Drug Side Effects and the Double-Blind Design

SIR: In a double-blind crossover trial reported by Joseph P. McEvoy, M.D., and associates (1), the anticholinergic drug trihexyphenidyl caused significantly more impairment of recall and recognition than did amantadine. Dry mouth was worse after trihexyphenidyl than after amantadine in 35% of the subjects, dizziness in 40%, toxic confusion in 28%, and nausea in 23%, but the investigators forgot the importance of submitting such differences to tests of statistical significance. There was no recognition of the possible effect of such side effects on the so-called double-blind design of the study and on the assertion that "no information regarding side effects or dose reduction was available to the psychological examiner who administered the test batteries." Epistemologically, that statement is a wish, since clearly the aforementioned side effects may well have been apparent to the examiner. However, since neither the design of the trial nor the review process that led to publication of the article by Dr. McEvoy and associates recognized the need for the purportedly double-blind design to be tested empirically—in this instance through guesses by the examiner about each patient's drug assignment, which would then be compared statistically with those to be expected by chance—the issue must remain apocryphal. Some of the test procedures involved reading and writing. A side effect of anticholinergic drugs is blurring of vision, so it was shortsighted not to discuss a possible connection between these side effects and performance on the tests.

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Dr. McEvoy and Associates Reply

SIR: Dr. Robinson states that we did not submit the different frequencies of side effects between the two treatment phases to tests of statistical significance. In fact, the anticholinergic side effects were indeed highly significantly associated with the use of trihexyphenidyl (by logistic regression). Since the central focus of the study was a comparison of effects on memory, we did not report the results of other unplanned statistical tests. Further, the level of severity of side effects was not generally high, and we did not wish to overstate the importance of finding anticholinergic side effects in subjects taking an anticholinergic drug.

Dr. Robinson states that detection of peripheral anticholinergic side effects could have compromised the blindness of the examiner who administered the memory tests. In an effort to avoid such compromise, we hired a psychological examiner who was naive to issues of anticholinergic toxicities, and we trained this individual solely to administer the memory tests and self-report batteries. At every assessment point, the principal investigator questioned each subject about untoward drug reactions, completed the side effects checklists, and made decisions about dose reduction. Subjects were then taken to the psychological examiner's office, which was on another floor, for memory testing. The psychological examiner was never made aware of the side effect profiles or dose reductions, and the principal investigator was not aware of a subject's performance on memory testing until completion of the entire protocol.

Dr. Robinson states that we failed to test empirically the completeness of the double-blind design, since we did not ask raters to guess subjects' drug assignments. We believe that asking raters to guess invites them to cheat if they can and that such tests of whether a blind is perfect have dubious merit. The only thing a double-blind design purports to do is place an element of doubt in the rater's mind regarding the drug assignment.

Dr. Robinson states that we did not discuss the possible effects of blurred vision on memory test performance. When present, blurred vision was mild. Subjects readily completed the Profile of Mood States and Self-Rating of Memory Function Questionnaire, which required reading sentences in standard print and checking boxes; their responses on these scales demonstrated their significant preference for the amantadine phase over the trihexyphenidyl phase of the trial. On both free-recall and signal detection-recognition testing, subjects were first shown each word in large print on a flashcard for 2 seconds and asked to immediately say the word aloud to assure comprehension. After the free-recall word list was presented, subjects wrote down as many words as they could remember. After the signal detection-recognition word list was presented, subjects were again shown the same large-print flashcards, mixed among distractor-word flashcards, and asked to distinguish between initially presented and distractor words. We do not believe visual acuity was a significant factor in performance on these tests thus administered.

JOSEPH P. MCEVOY, M.D.
PHILIP W. LAVORI, PH.D.
MICHAEL MCCUE, PH.D.
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Animal Rights and Research

SIR: Regarding the editorial "The Animal Rights Movement: A Research Perspective" by Harold Alan Pincus, M.D., and colleagues (1), I am afraid the animal rights movement is an all too convenient "straw man." The basic issue has long been that the use of animals in psychiatric research is objectionable on purely scientific grounds. It was surely a curious alchemy that blended theories of Darwin, Koch, and Pavlov to create the "animal model of human psychopathology." Nonetheless, has animal research led to major advances in the treatment of mental illness. The clearest advances in the treatment of mental illness are those that have been validated in controlled trials. Except for the antidepressants and antipsychotics, there are few treatments for mental illness that have been so validated.

How then were the antidepressants and antipsychotics really discovered? Applying Occam's razor to medical history, it is only possible to arrive at one answer: the antidepressants and antipsychotics were discovered by clinical serendipity. This was common knowledge among psychopharmacologists until Miller (2) and other animal research enthusiasts started rewriting medical history.

Even the sedative effects of the phenothiazines were first seen in man. In following up the promethazine lead, chlorpromazine was developed as a preanesthetic sedative, but what a surprise when it turned out to have dramatic effects on mood in human patients! Psychopharmacologists should recall that there was no hint of even the sedative effect in most early animal studies with phenothiazines (3, p. 27). It is (or was) also well-known that many, if not most, of the major antidepressants would have been discarded on the basis of animal tests (4).

Rather than erecting the straw man of "antivivisectionism," Dr. Pincus and his colleagues would do well to create an atmosphere in which the scientific legitimacy of much animal work could be openly debated. As far back as 1952, Peller (5) recognized the need for such debate when he wrote, "The overestimation of animal experiment is so rampant that the issue is of general interest" (p. 88). More important, a clear-eyed analysis of medical history leads to immediate implications for psychoactive drug development.

Rather than continuing with excessive requirements for premarket testing, the regulatory agencies should maximize the potential for clinical serendipity. At the same time, surveillance systems should be set up for monitoring the *therapeutic* side effects of drugs that are already on the market. The nation's best-known clinical pharmacologist, Dr. Kenneth Melmon, made just such a recommendation as chairman of the Joint Commission on Prescription Drug Use in 1980, but could not get the $10 million necessary to launch the program (6). The Medical Research Modernization Committee, of which I am acting medical director, with its 650 members, hopes to facilitate such public health research by promoting computerized surveillance systems. Real-world problems require real-world solutions.

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BRANDON P. REINES, D.V.M.
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SIR: The work of Alan R. Felthous, M.D., and Stephen R. Kellert, Ph.D. (1) demonstrates very well that animals act as the recipients both of projected impulses and of aggression itself, telling us much about how aggression is modulated. Eventually, our psychiatric observations will butt heads with our political activities. For while we are discovering that repeated aggression toward animals indicates characterologic problems, we gloss over the most systematized aggressions toward animals, that is, those done in the name of science.

The editorial by Dr. Pincus and associates, which preceded the Felthous and Kellert article by 6 months, was an essentially political defense of animal experimentation. A moment's reflection will tell us that intrapsychic issues undoubtedly play a role in experimentation, too.

Shall we recognize the psychiatric variables played out in animal abuse on the streets while suspending any inquiry into the variety of motivations and cultural and superego failures that allow it to go on nearly unquestioned in laboratories?

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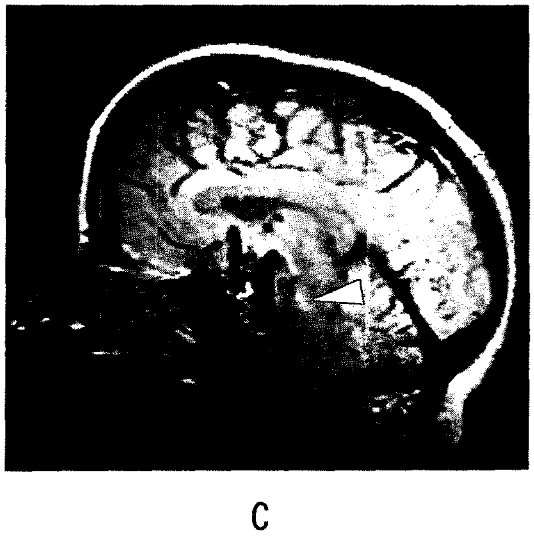
Correction

In the article "Use of Magnetic Resonance Imaging in Psychiatry" (February 1988 issue, pp. 164–171) by H. Jordan Garber, M.D., et al., on p. 169, right column, first full paragraph, twelfth line, TI should have been T_1. Also, there should have been an arrow on photograph c of figure 2 on p. 166. The corrected photograph is shown below.

FIGURE 2(c). MRI Case 2: Midline Sagittal Spin-Echo Image[a]



[a] The image shows abnormal area in pons (arrow).

Reprints of letters to the Editor are not available.

Official Actions

AIDS Policy: Confidentiality and Disclosure

This policy was drafted by the Ad Hoc Committee on AIDS Policy[1] and was approved by the Board of Trustees in December 1987.

Introduction

The epidemic of acquired immune deficiency syndrome (AIDS) presents difficult and perplexing issues, many of which involve conflicts between the rights of infected individuals and the society's interest in containing the epidemic. Because these questions are highly controversial and because so many important scientific questions about the disease remain unanswered, a definitive public health strategy has not yet emerged.

Physicians have an important role in controlling human immunodeficiency virus (HIV) infection. However, for physicians, the care and treatment of individual patients is of the utmost importance. Patients must be confident that the issues discussed with their physicians are private and will not be unnecessarily divulged. Certainly, any breach of confidentiality should be a last resort, only after scrupulous attention has been given to all other alternatives.

At the present time, the operational public health strategy promotes voluntary testing while eschewing programs of contact tracing, surveillance, segregation, and other measures that could discourage people from seeking testing. Many troublesome ethical and clinical questions arise in the context of dealing with individual patients, and the purpose of this document is to provide some guidance to members of the profession as they struggle to honor their duty to preserve the confidences of their patients while taking adequate precautions to protect persons who may be at risk of contracting the disease.

Physicians should be aware that state laws may restrict some of the actions recommended in these guidelines. Where conflict exists, attempts should be made to modify the laws in accordance with the principles expressed herein.

Confidentiality

Physicians have an ethical obligation to recognize the rights to privacy, to confidentiality, and to informed consent of all patients. During the initial clinical evaluation, the physician should usually make clear the general limits of confidentiality. If the physician has reason to suspect the patient is infected with HIV (e.g., seropositive) or is engaging in behavior that is known to transmit HIV disease, the physician should notify the patient of the specific limits of confidentiality. Furthermore, if the physician intends to inquire specifically about the HIV status of a given patient, then the physician should notify the patient about the limits of confidentiality before asking such questions.

Notification of Third Parties

In situations where a physician has received convincing clinical information (the patient's own disclosure of test results or documented test records) that the patient is infected with HIV, the physician should advise and work with the patient either to obtain the patient's agreement to terminate behavior that places other persons at risk of infection or to notify identifiable individuals who may be at continuing risk of exposure. If a patient refuses to agree to change his or her behavior or to notify the person(s) at risk or the physician has good reason to believe that the patient has failed to or is unable to comply with this agreement, it is ethically permissible for the physician to notify an identifiable person who the physician believes is in danger of contracting the virus.

Disclosure to Third Parties

Most states now require physicians to report cases in which they diagnose AIDS to a public health agency; only a few require the reporting of cases of individuals who test positive for HIV. It is ethically permissible for a physician to report to the appropriate public health agency the name of a patient who has been determined by convincing clinical information (the patient's disclosure of test results or documented test records) to be infected with HIV and who the physician has good reason to believe is engaging in behavior that places other persons at risk of HIV infection. Although we recognize that public health agencies have varying responses to the problem at the present time, provision of this information will allow them to take whatever measures they regard as appropriate.

---

[1] The committee includes Robert O. Pasnau, M.D. (chairperson), Elissa Benedek, M.D., Dorothy A. Starr, M.D., James Krajeski, M.D., Stuart E. Nichols, M.D., Howard Zonana, M.D., Francisco Fernandez, M.D., Patrick Staunton, M.D., Henry Work, M.D., and Marvin Stein, M.D.

AIDS Policy: Guidelines for Inpatient Psychiatric Units

This policy was drafted by the Ad Hoc Committee on AIDS Policy[1] and was approved by the Board of Trustees in December 1987.

Patient Care

All available evidence indicates that acquired immune deficiency syndrome (AIDS) is a disease of low transmissibility in the medical setting. Education and counseling regarding transmission of the human immunodeficiency virus (HIV) continue to be needed and should be available to physicians and other medical personnel. Historically, physicians and other medical personnel have been exemplary in the treatment of patients, even in situations of personal risk, and it is expected that this tradition will continue.

1. All psychiatric patients should be treated on the basis of their clinical conditions; neither HIV infection nor serologic status should, in and of itself, impede the delivery of appropriate medical-psychiatric treatment.
2. HIV serological testing should be performed on a case-by-case basis and with informed consent when medically indicated. HIV serological testing should not be performed solely for the purpose of routine screening or staff awareness.
3. Regardless of HIV serologic status, all inpatients should be considered potentially at risk for transmitting or receiving HIV infection. A minimal standard of care should include a) implementation and monitoring of the infection control procedures outlined in the current standards of the Centers for Disease Control (CDC), b) appropriate management of affective, cognitive, and behavioral disturbances to ensure risk reduction for both patients and personnel, and c) appropriate education and supportive services for patients, families, and staff.
4. If a patient known to be infected with HIV engages, or threatens to engage, in behavior that places other individuals at risk, the responsible physician should assure that appropriate clinical steps are taken to control the behavior and, if necessary, isolate and/or restrain the patient.

Disclosure

Once a patient has been hospitalized on a psychiatric unit and responsibility for the patient's care has been assumed, the need to protect other patients and staff from foreseeable dangerous behavior arises. In the situation where a particular patient is known to be HIV positive, the following additional guidelines are recommended.

1. Deciding whether to disclose a patient's HIV infection to other staff is a delicate clinical question. The responsible physician should disclose the information to the appropriate staff only after discussions with the patient, if the physician determines that appropriate treatment of the patient requires such disclosure.
2. If the patient engages in behavior likely to transmit the virus and there is a significant risk that such behavior cannot be controlled by other measures, then disclosure of a patient's infectious condition to other patients at risk is permissible. Disclosure is not a substitute for adequate clinical care and is usually inappropriate for the physician or staff to disclose a patient's HIV infection to other patients.

Discharge

When discharge is otherwise clinically appropriate, if the patient represents a substantial risk to others by virtue of behavior known to transmit the virus but this danger is not related to a specific mental condition, it is inappropriate to retain the person in the hospital solely for quarantine or preventive detention.

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[1] The committee includes Robert O. Pasnau, M.D. (chairperson), Elissa Benedek, M.D., Dorothy A. Starr, M.D., James Krajeski, M.D., Stuart E. Nichols, M.D., Howard Zonana, M.D., Francisco Fernandez, M.D., Patrick Staunton, M.D., Henry Work, M.D., and Marvin Stein, M.D.

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Columbia University, College of Physicians and Surgeons
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Psychiatric Aspects of AIDS
Frederick K. Goodwin, MD
Director, Intramural Research
National Institute of Mental Health
Bethesda, MD

A New Look at the Old Dopamine Hypothesis
Daniel R. Weinberger, MD
Chief, Clinical Brain Disorder Branch
National Institute of Mental Health
Washington, DC

New Horizons for Genetics and Mental Illness
Nancy S. Wexler, PhD
Associate Professor of Clinical Neuropsychology
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Neurobiological Mechanisms of Human Anxiety
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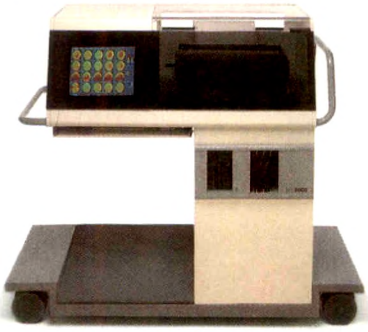

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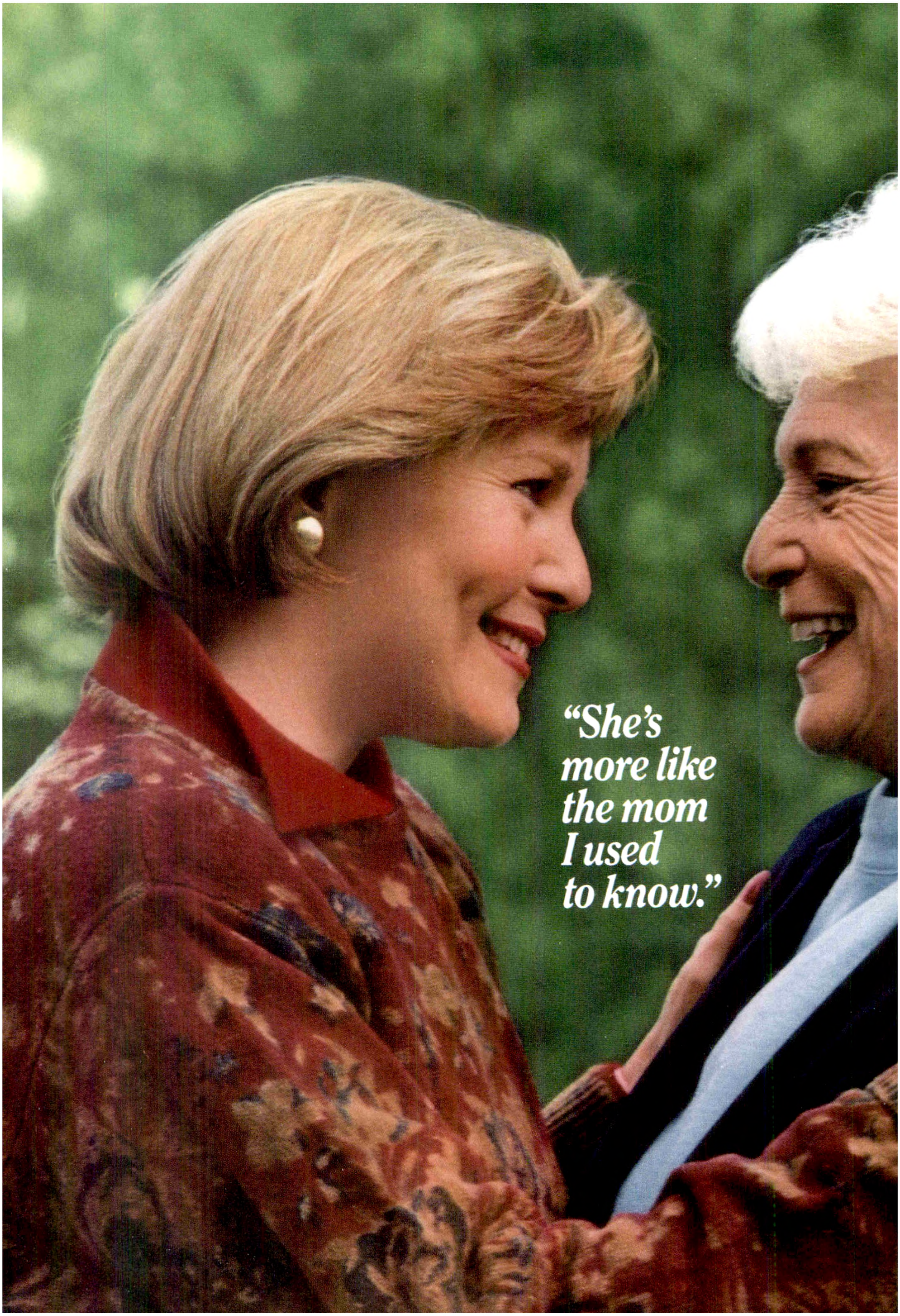
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WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop, after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative, effective, less harmful treatments are *not* available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)

This potentially fatal symptom complex has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnostic evaluation is complicated; it is important to identify both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

Management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. Carefully consider the potential reintroduction of drug therapy in patients requiring antipsychotic drug treatment after recovery from NMS since recurrences have been reported. Such patients should be monitored.

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine hydrochloride cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn. Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine.

ADVERSE REACTIONS: *Central Nervous System:* Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue pro-

References:

1. Raskind MA, Risse SC: Antipsychotic drugs and the elderly. J Clin Psychiatry 47 (suppl to no. 5): 17-22, 1986.
2. Steinhart MJ: Pharmacological considerations in the use of high-potency neuroleptics in elderly patients. Geriatr Med Today 3(2): 65-73, 1984.
3. Salzman C: Treatment of the elderly agitated patient. J Clin Psychiatry 48 (suppl to no. 5): 19-22, 1987.
4. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 221, 222.

Please see brief summary continuing on adjacent page.

Continued from preceding page.

trusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

Other CNS Effects: Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occur, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage as manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed sudden flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates, and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines.

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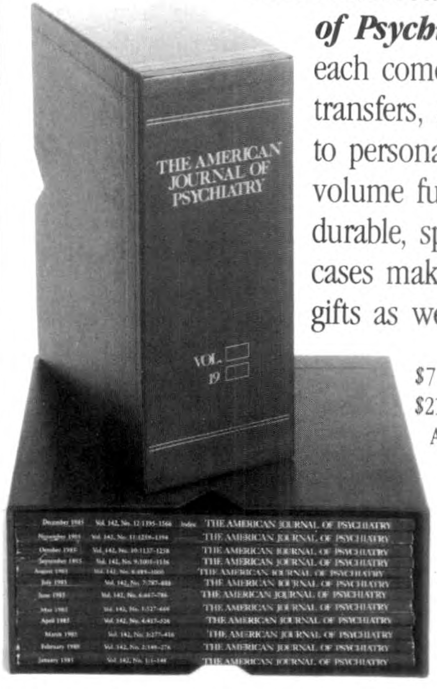

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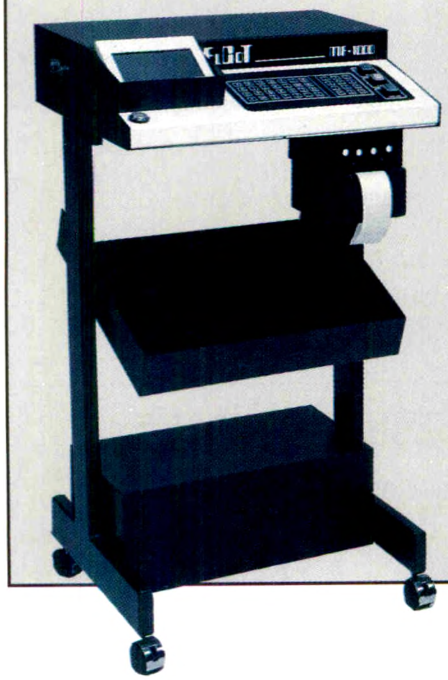

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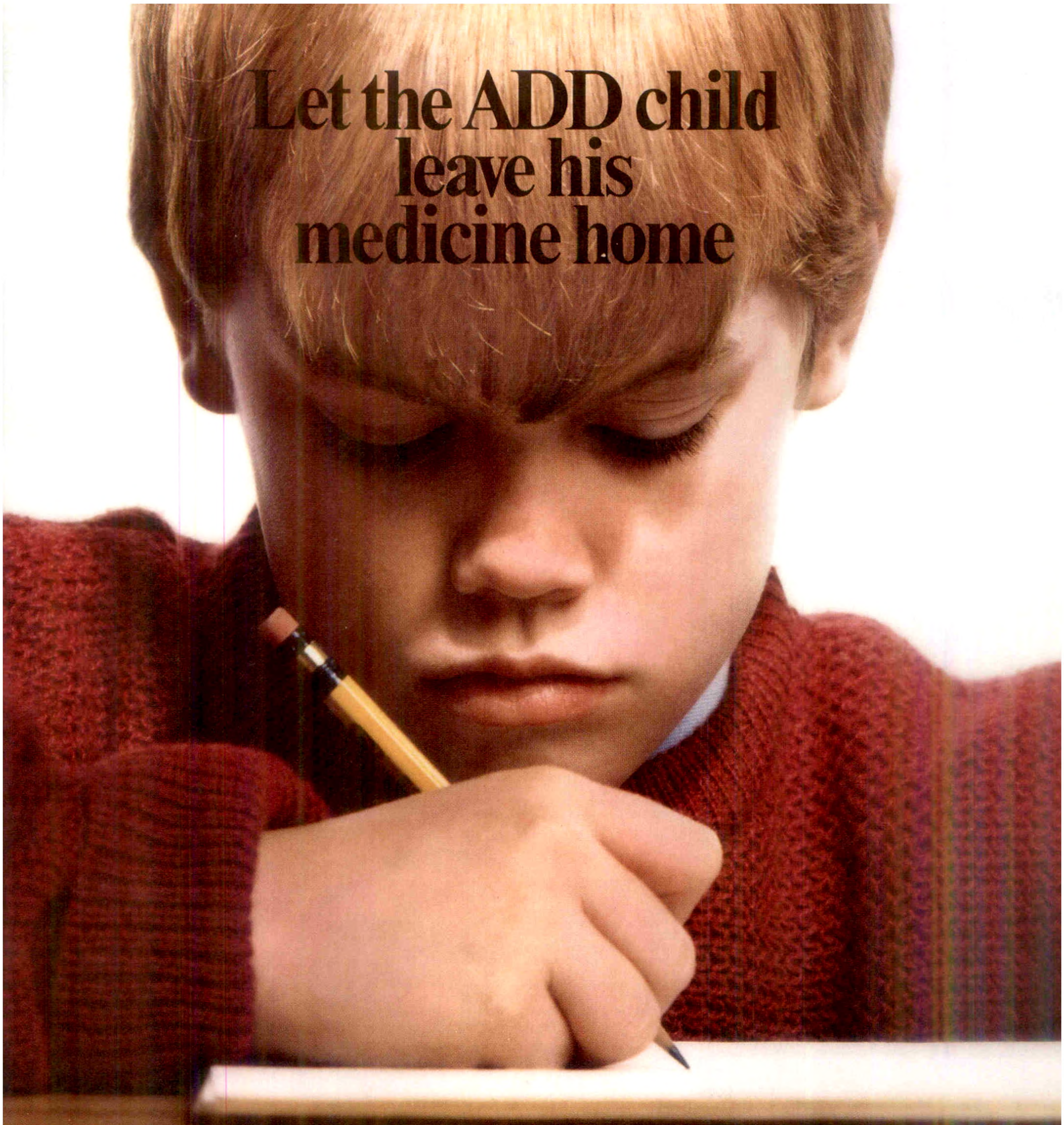

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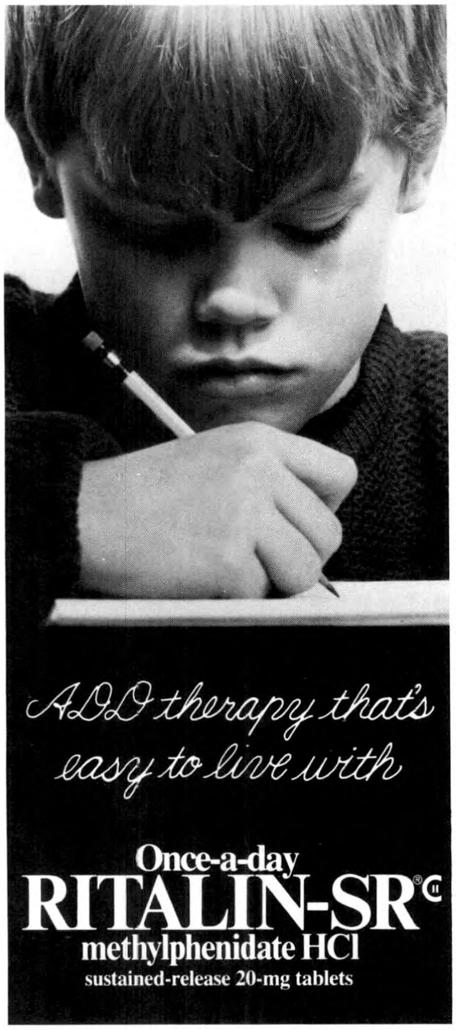
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INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie,* weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

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Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage ad
justment over a one-month period, the drug should be discontinued.

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If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the dr
is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principal
from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the followin
vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyper
rexia, tachycardia, palpitations, cardiac arrhythmias, hyperten
sion, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. Th
patient must be protected against self-injury and against exte
nal stimuli that would aggravate overstimulation already present. If signs and symptoms are not too severe and the pa
tient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of seve
intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Intensive care must be provided to maintain adequate circu
tion and respiratory exchange; external cooling procedures m
be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialys
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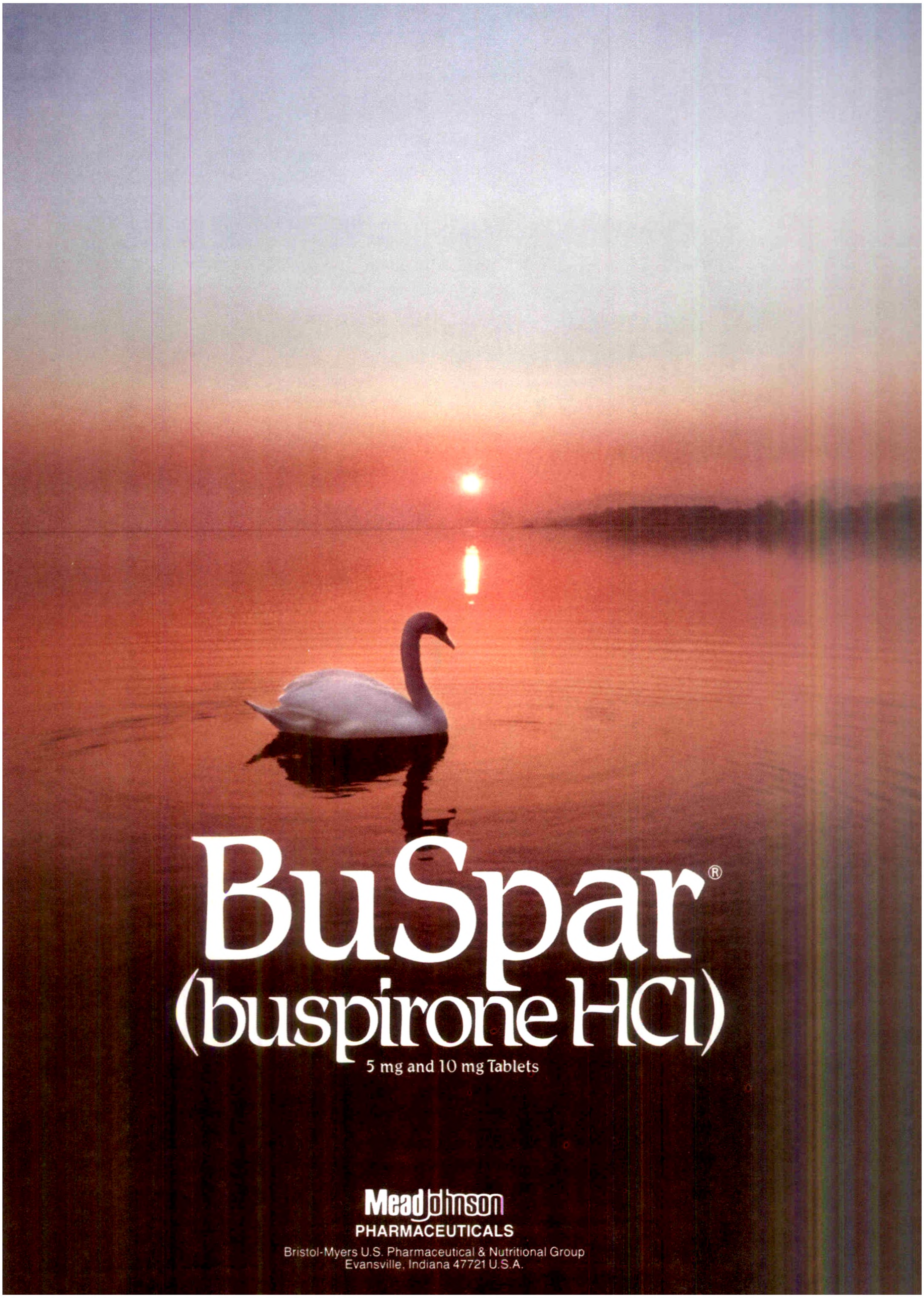

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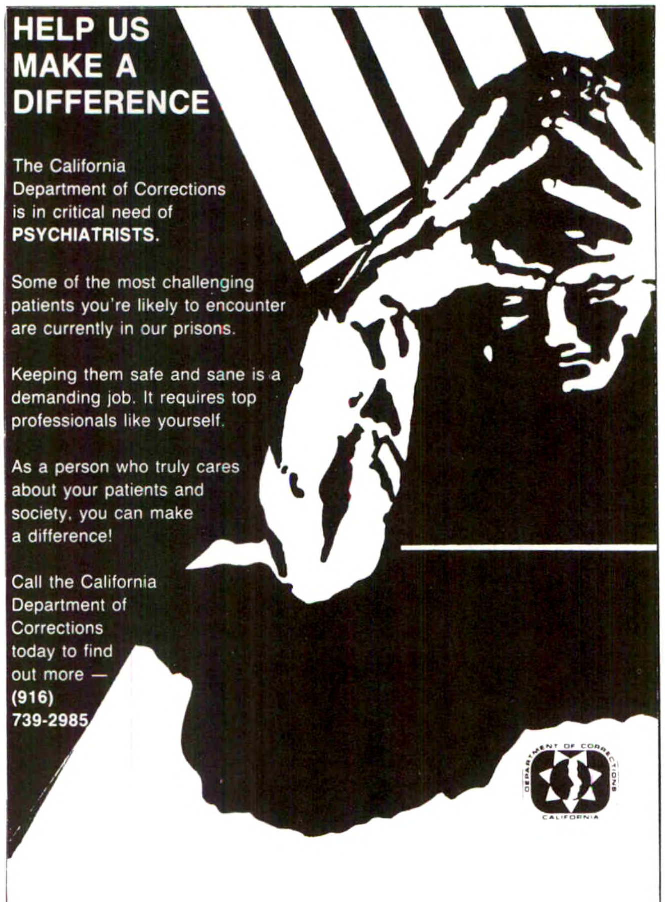

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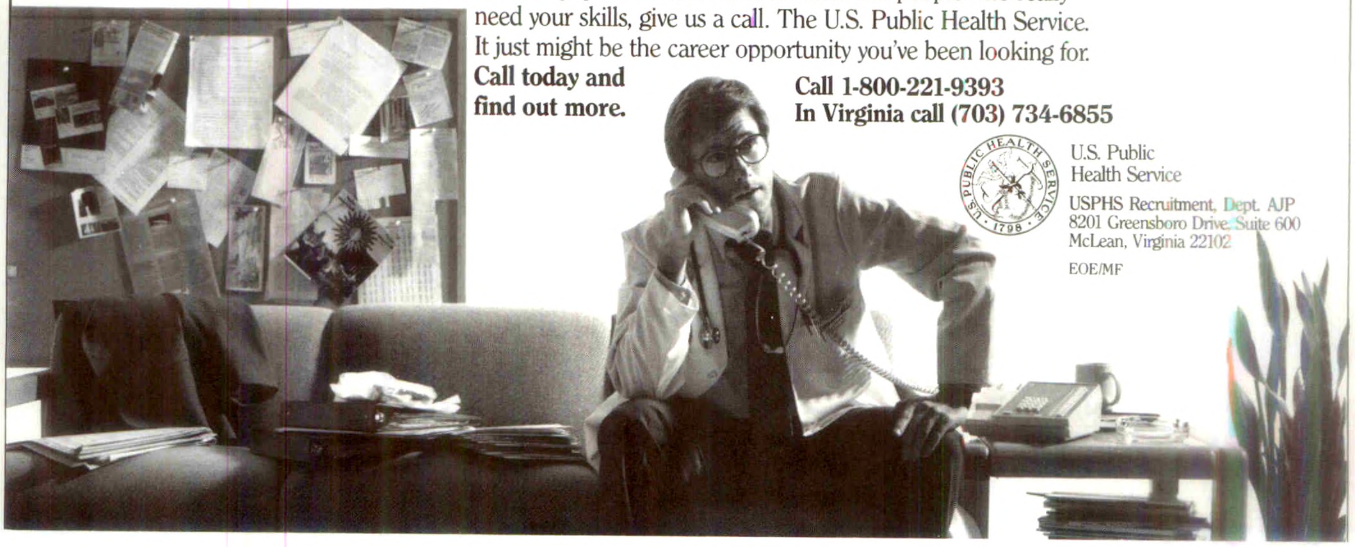

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Privatization of Psychiatric Services
By Robert A. Dorwart and Mark Schlesinger

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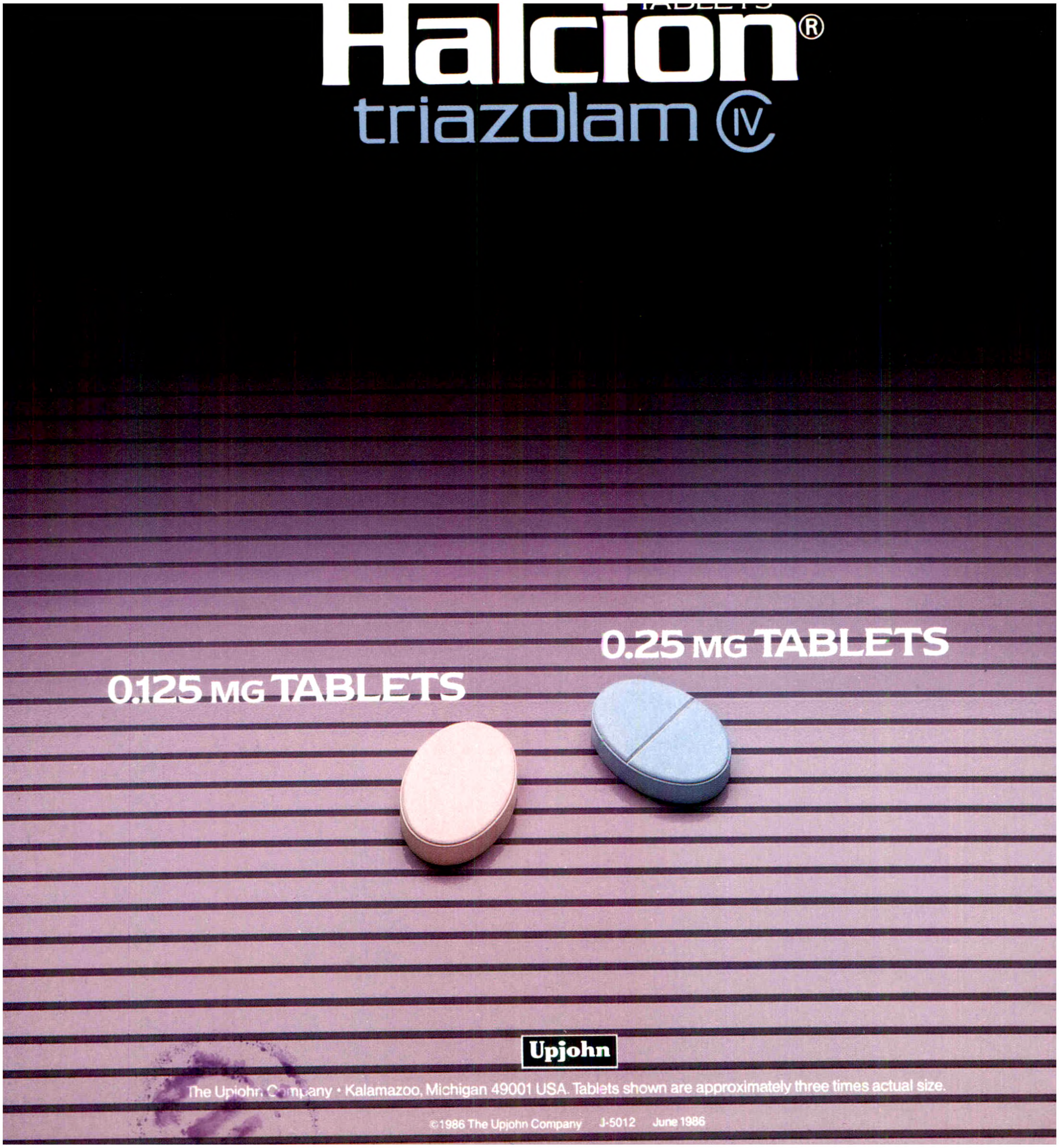

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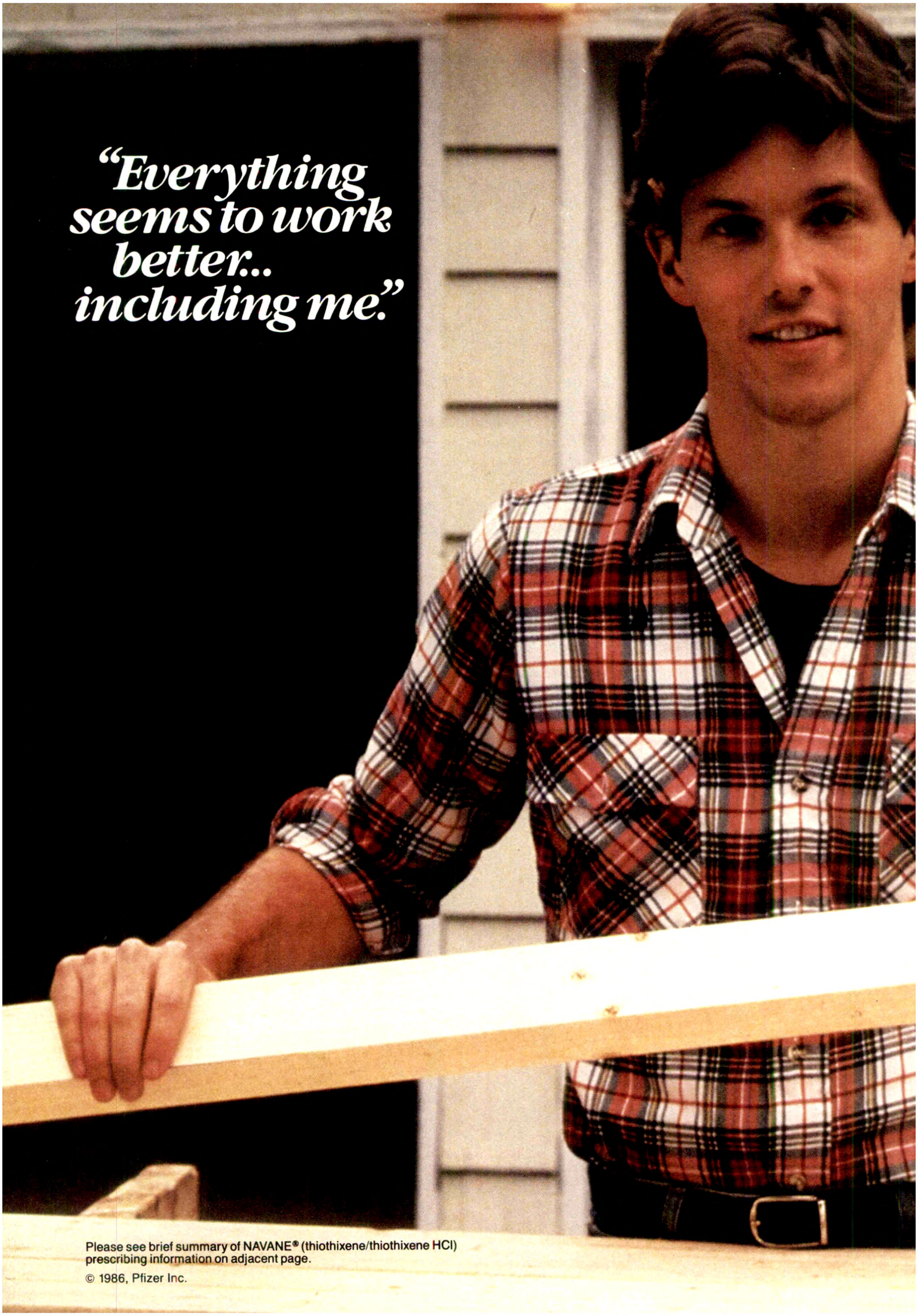
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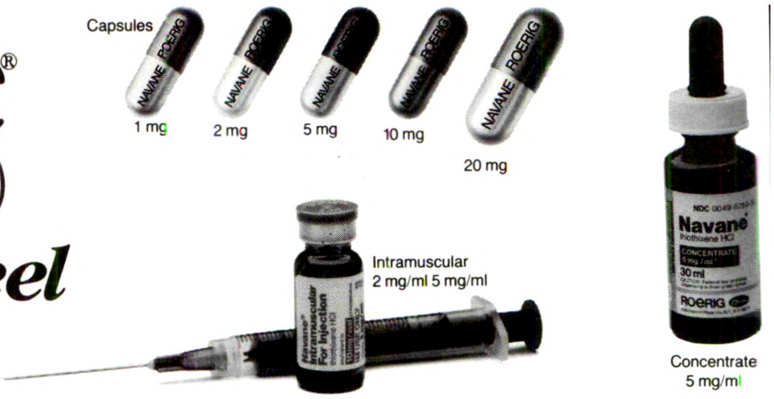

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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver dama (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patie on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadr of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to h avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tis culture experiments indicate that approximately one third of human breast cancers are prolactin-depend *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gyne mastia, and impotence have been reported, the clinical significance of elevated serum prolactin level unknown for most patients. An increase in mammary neoplasms has been found in rodents after chro administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to da however, have shown an association between chronic administration of these drugs and mammary tum igenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be giver possible, full information about this risk. The decision to inform patients and/or their guardians must viously take into account the clinical circumstances and the competency of the patient to understand information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Nav (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the pheno azines, all of the known side effects and toxicity associated with phenothiazine therapy should be born mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypot sion occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of bl pressure may result. Nonspecific EKG changes have been observed in some patients receiving Nav (thiothixene). These changes are usually reversible and frequently disappear on continued Navane thera The incidence of these changes is lower than that observed with some phenothiazines. The clinical sig cance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuatio Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazin but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been no with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Nav infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally rela drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal f abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been report Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of ac symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in so patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrom characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusio tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be acc panied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing sis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndro If this or any other presentation of the syndrome is observed, the clinician should consider possible disc tinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, been infrequently observed in some patients. No clinically confirmed cases of jaundice attributabl Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocyto which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been sociated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with cer phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a s percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, necomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating creased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothia therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNI section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phen azine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to fa of the cough reflex. In others, the cause could not be determined nor could it be established that death due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity o condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescri information.

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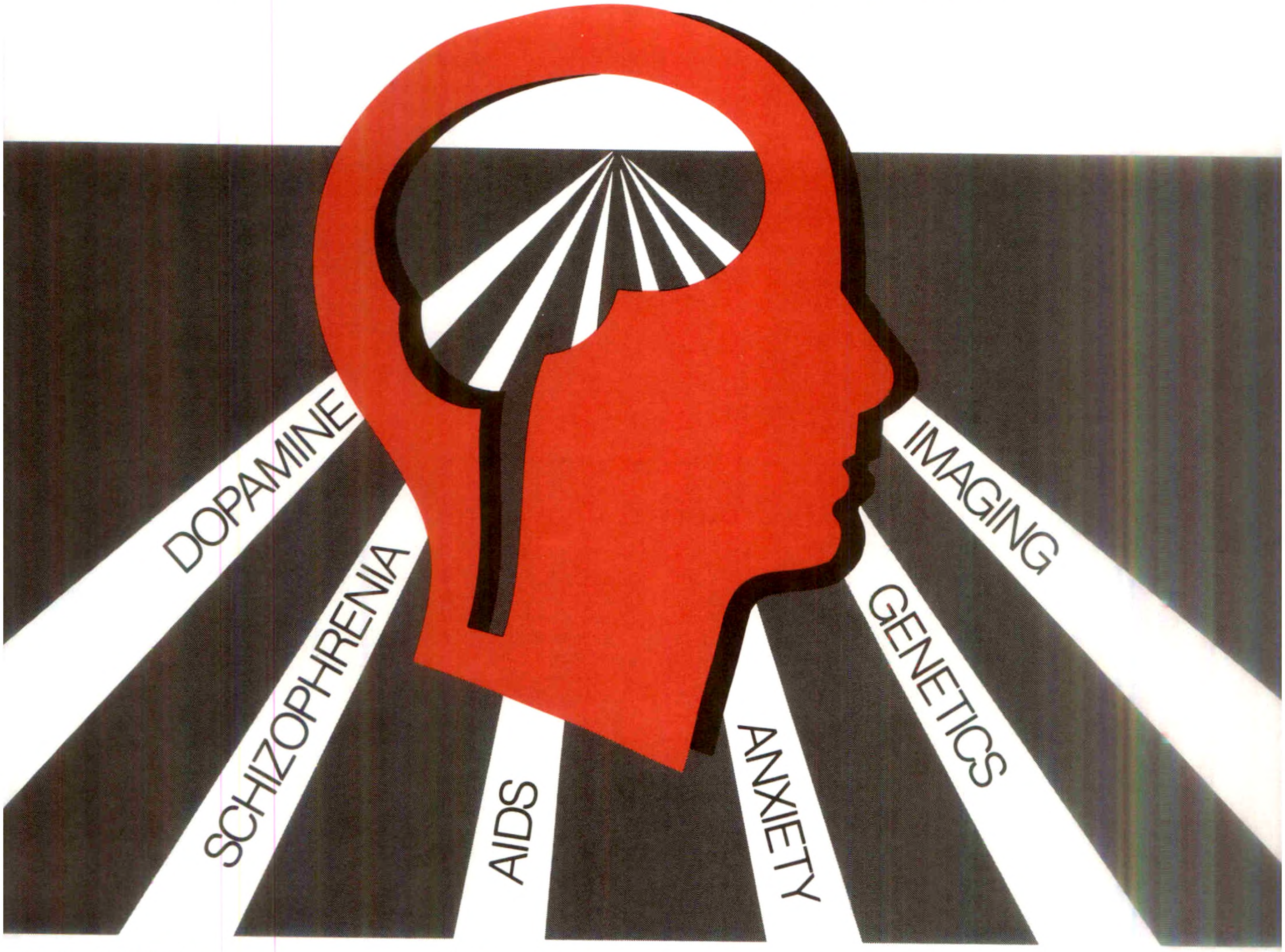

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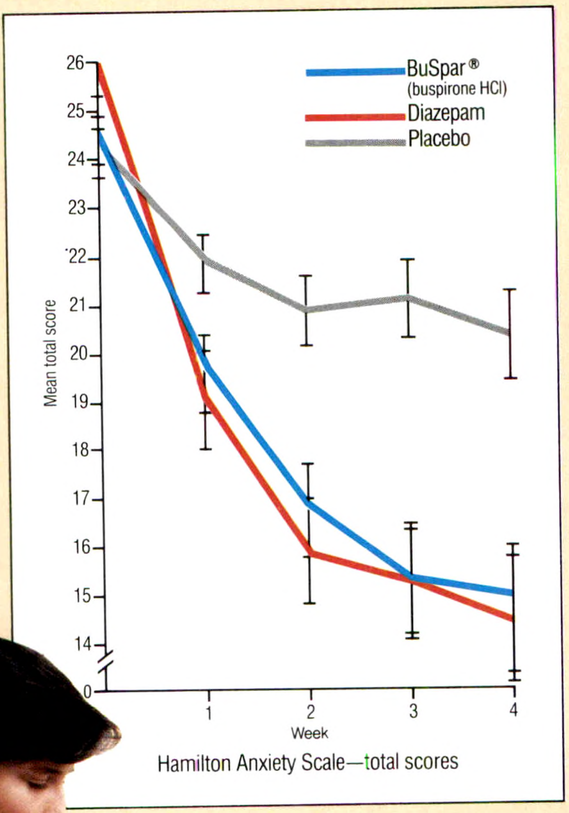
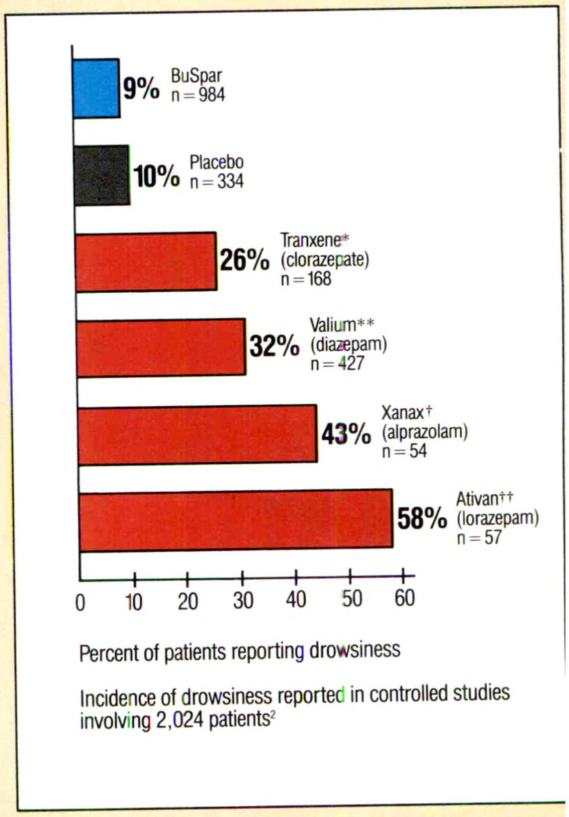


Hamilton Anxiety Scale—total scores

...with no more drowsiness than placebo[2]



Percent of patients reporting drowsiness

Incidence of drowsiness reported in controlled studies involving 2,024 patients[2]

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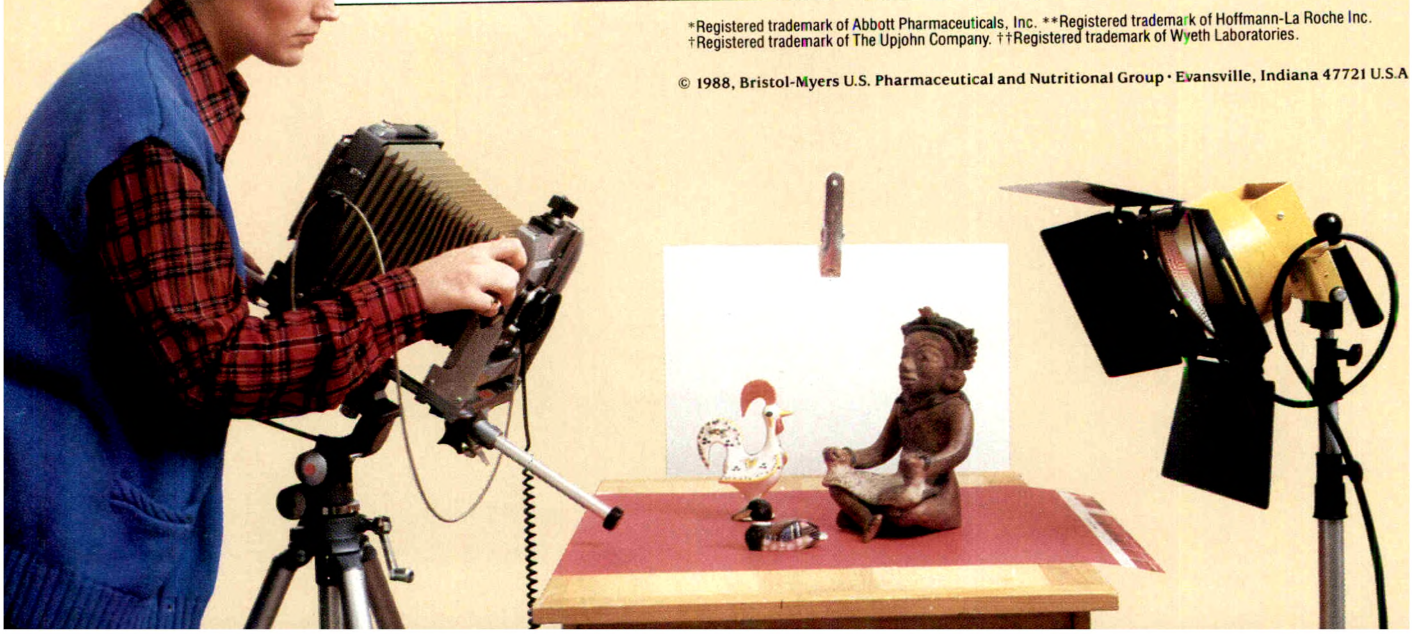

The first choice for chronic anxiety

BuSpar effectively relieves the symptoms of anxiety—such as irritability, inability to concentrate, and excessive worry—without producing significant sedation[2] or euphoria.[3]

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Counseling and follow-up are important. Patients should be advised that BuSpar does not produce a tranquilizer "buzz," but instead will relieve their symptoms gradually and steadily. Improvement generally is noted within 7 to 10 days. Patients should be monitored for relief of symptoms, improvement in functioning, and an increased capacity to cope.

BuSpar is not a controlled substance. The most common side effects noted in controlled clinical trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

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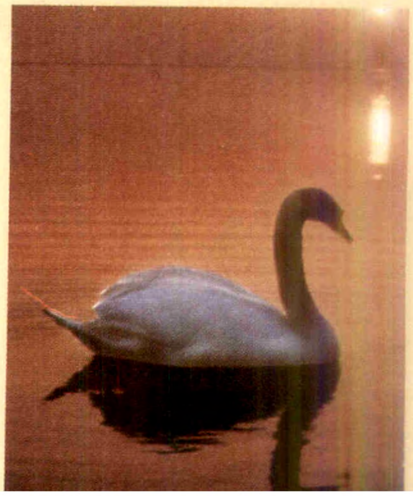

For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

References: 1. Rickels K, *et al*: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12,Sec 2):81-86. **2.** Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(Suppl 3B):17-21. **3.** Cole JO, *et al*: Assessment of the abuse liability of buspirone in recreational sedative users. *J Clin Psychiatry* 1982;43(12,Sec 2):69-74. **4.** Lucki I, *et al*: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **5.** Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **6.** Mattila MJ, *et al*: Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;43(12,Sec 2):56-60. **7.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(Suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, light-headedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, light-headed feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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"There is considerable evidence that serotonergic function may be reduced in the brains of depressed patients."
Arch Gen Psychiatry 1984;41:398-402.
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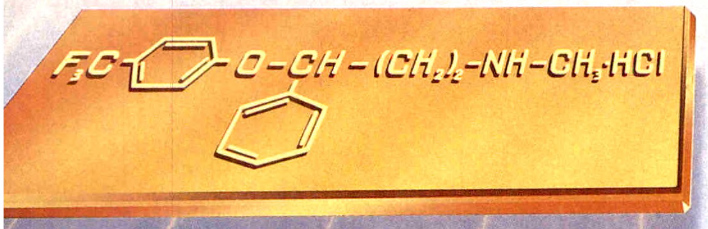

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greater specificity.

The first highly specific…highly potent blocker of serotonin uptake

Effective treatment for depression

Fewer side effects to disrupt therapy

Side effects with Prozac® (fluoxetine hydrochloride) **are generally mild and manageable and include nausea, anxiety/nervousness, insomnia, and drowsiness**

Rash and/or urticaria occurred in 4% of clinical trial patients

Wide margin of safety

20-mg once-a-day therapy

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New York, NY 10150

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Rash and Accompanying Events*—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substanccs. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event Prozac (N=1,730)	Percentage of Patients Reporting Event Placebo (N=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

---

*Events reported by at least 1% of Prozac patients are included.
—Incidence less than 1%.

Prozac® (fluoxetine
hydrochloride, Dista)

Other Events Observed During the Premarketing Evaluation of Pr
During clinical testing in the US, multiple doses of Prozac were a
tered to approximately 5,600 subjects. Untoward events associat
this exposure were recorded by clinical investigators using des
terminology of their own choosing. Consequently, it is not pos
provide a meaningful estimate of the proportion of individuals exper
adverse events without first grouping similar types of untoward eve
a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionar
nology has been used to classify reported adverse events. The freq
presented, therefore, represent the proportion of the 5,600
exposed individuals who experienced an event of the type cited on
one occasion while receiving Prozac. All reported events are i
except those already listed in tables, those COSTART terms so gene
be uninformative, and those events where a drug cause was rem
important to emphasize that, although the events reported did occu
treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and
ated in order of decreasing frequency using the following def
frequent adverse events are defined as those occurring on one
occasions in at least 1/100 patients; infrequent adverse events a
occurring in 1/100 to 1/1,000 patients; rare events are those occ
less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, c
edema, hangover effect, jaw pain, malaise, neck pain, neck rigi
pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, h
mia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina pectoris, arrhythm
orrhage, hypertension, hypotension, migraine, postural hypotensi
cope, and tachycardia; *Rare:* AV block (first-degree), brad
bundle-branch block, cerebral ischemia, myocardial infarct,
bophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:* a
stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis
tis, liver function tests abnormal, melena, stomatitis, and thir
bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulc
itis, fecal incontinence, hematemesis, hepatitis, hepatomegal
chlorhydria, increased salivation, jaundice, liver tenderness
ulceration, salivary gland enlargement, stomach ulcer, tongue
oration, and tongue edema.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* goiter ar
thyroidism.

Hemic and Lymphatic System—*Infrequent:* anemia and lymph
athy; *Rare:* bleeding time increased, blood dyscrasia, leukoper
phocytosis, petechia, purpura, sedimentation rate increased, an
bocythemia.

Metabolic and Nutritional—*Frequent:* weight loss; *Infrequen*
alized edema, hypoglycemia, peripheral edema, and weight ga
dehydration, gout, hypercholesteremia, hyperglycemia, hype
hypoglycemic reaction, hypokalemia, hyponatremia, and iron d
anemia.

Musculoskeletal System—*Infrequent:* arthritis, bone pain,
tenosynovitis, and twitching; *Rare:* bone necrosis, chondrod
muscle hemorrhage, myositis, osteoporosis, pathological frac
rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitatio
quent: abnormal gait, acute brain syndrome, akathisia, amnesia
ataxia, buccoglossal syndrome, CNS stimulation, convulsion, d
depersonalization, emotional lability, euphoria, hallucinations,
hyperkinesia, hypesthesia, incoordination, libido increased, ma
tion, neuralgia, neuropathy, paranoid reaction, psychosis, and
Rare: abnormal electroencephalogram, antisocial reaction, chr
syndrome, circumoral paresthesia, CNS depression, coma, dy
dystonia, extrapyramidal syndrome, hypertonia, hysteria, myocl
stagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent:* bronchitis, rhinitis, and yaw
quent: asthma, epistaxis, hiccup, hyperventilation, and pneumo
apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung
alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact de
dry skin, herpes simplex, maculopapular rash, and urticar
eczema, erythema multiforme, fungal dermatitis, herpes zoster, h
psoriasis, purpuric rash, pustular rash, seborrhea, skin discolora
hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* ambylopia, conjunctivitis, ear
pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis,
corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, i
sis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, ame
breast pain, cystitis, dysuria, fibrocystic breast, impotence, le
menopause, menorrhagia, ovarian disorder, urinary incontinenc
retention, urinary urgency, urination impaired, and vaginitis; *R*
tion, albuminuria, breast enlargement, dyspareunia, epididymit
lactation, hematuria, hypomenorrhea, kidney calculus, met
orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral
thritis, urinary tract disorder, urolithiasis, uterine hemorrhag
spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there
deaths among approximately 38 reports of acute overdose with f
either alone or in combination with other drugs and/or alcohol.
involved a combined overdose with approximately 1,800 mg of
and an undetermined amount of maprotiline. Plasma concent
fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L resp
second death involved three drugs yielding plasma concent
follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; cod
mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxeti
enced two grand mal seizures that remitted spontaneously witho
anticonvulsant treatment (*see* Management subsection). T
amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involv
fluoxetine doses. Other prominent symptoms of overdose inclu
tion, restlessness, hypomania, and other signs of CNS excitati
for the two deaths noted above, all other overdose cases recover
residua.

PV 2150 DPP

Prozac® (fluoxetine
hydrochloride, Dista)

Additional information available to the profession on request fro

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Co-Chairperson Herbert Y. Meltzer, MD, Douglas D. Bond Professor of Psychiatry, Case Western Reserve University, School of Medicine, Department of Psychiatry

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- **Neuroleptic-Induced Movement Disorders...** identification and management options
- **The Therapeutic Profile of a New, Atypical Antipsychotic Agent**
- **The Neuroendocrine Profile of a New, Atypical Antipsychotic Agent**
- **A Brief Review of Drug-Induced Agranulocytosis**
- **Exploration of a New WBC Monitoring System**
- **Economic, Fiscal and Cost-Effectiveness Considerations**

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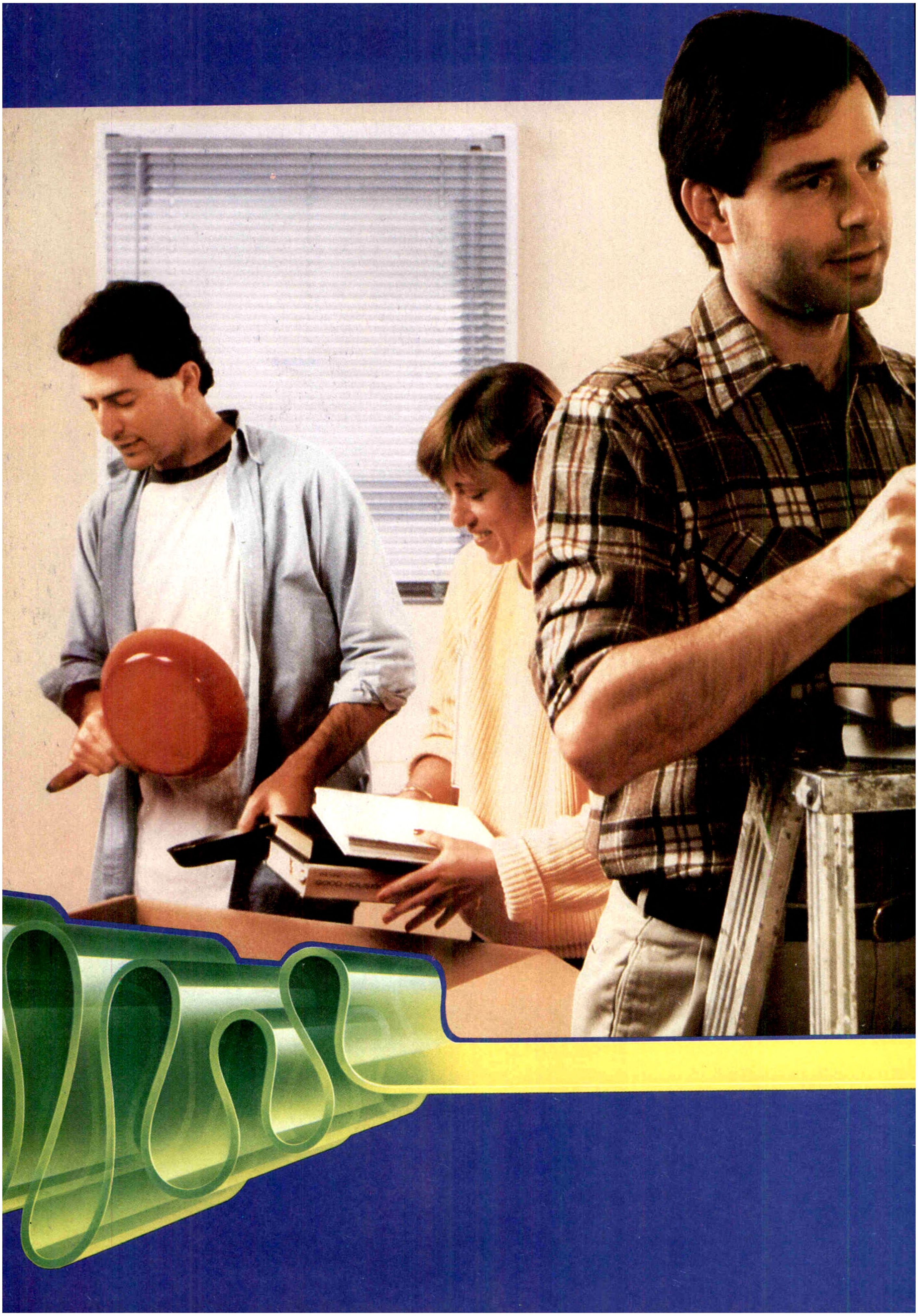

For the schizophrenic patient

Sustained protection from relapse

About 60% of schizophrenic patients will experience relapse at some time.[1] Because of the increased risk of deterioration with each relapse, today's therapeutic challenge is to use all available measures to prevent its occurrence.[2] The sustained drug delivery of once-monthly HALDOL Decanoate Injection can be one factor in reducing the risk of relapse. Monthly administration assures that patients receive the prescribed dose of medication.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

References:

1. Johnson DA: Epidemiological evaluation of maintenance antipsychotic treatment, in Tognoni G, Bellantuono C, Laher H (eds): *Epidemiological Impact of Psychotropic Drugs*. Amsterdam, Elsevier/North Holland Biomedical Press, 1981, pp 205-220.
2. Lehmann HE, Cancro R: Schizophrenia: clinical features, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry*, ed 4. Baltimore, Williams & Wilkins, 1985, vol 1, pp 680-713.

Please see brief summary of Prescribing Information on next page.

Once-monthly

HALDOL® DECANOATE
(HALOPERIDOL) INJECTION

McNEIL
PHARMACEUTICAL
McNEILAB, INC., Spring House, PA 19477

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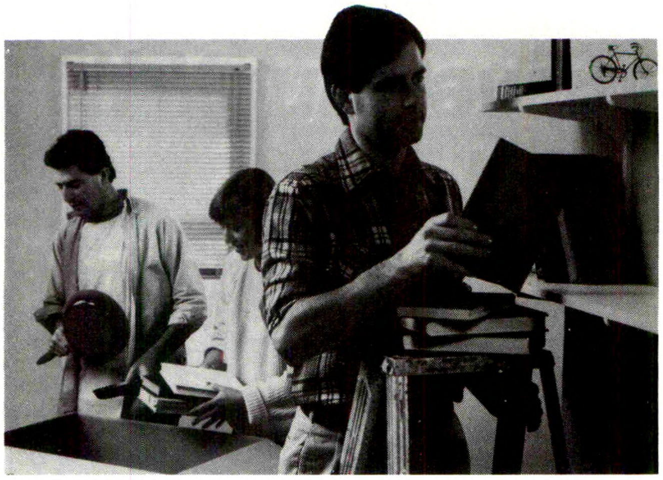

HALDOL® DECANOATE

(HALOPERIDOL) INJECTION

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

6/3/87

For additional information, please call:

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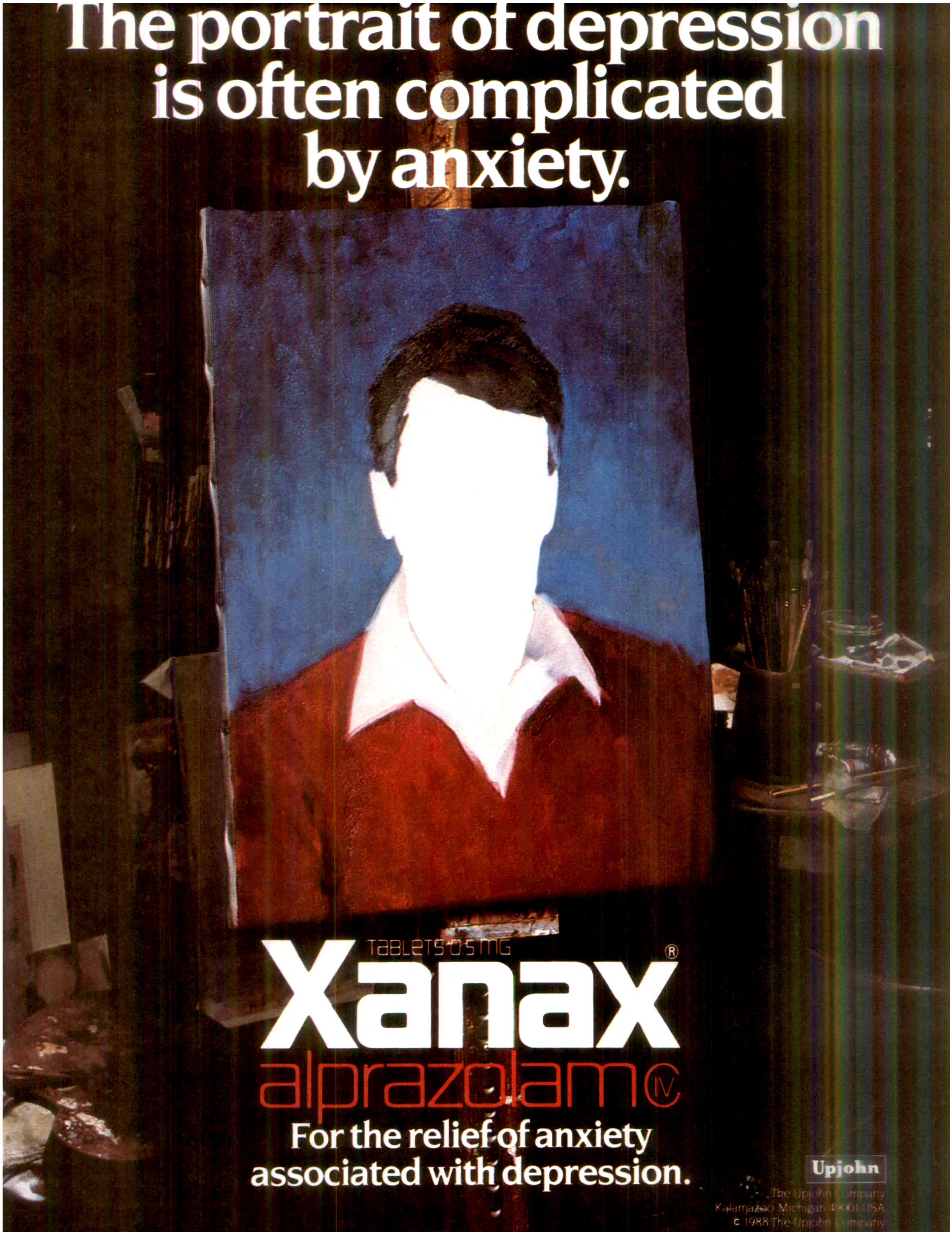
The portrait of depression is often complicated by anxiety.
TABLETS 0.5 MG
Xanax®
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For the relief of anxiety associated with depression.
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XANAX® Tablets
(alprazolam) Ⓒ

INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS

***General*:** If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

***Information for Patients*:** Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:

FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

JULY

July 5–7, annual meeting, Royal College of Psychiatrists, Brighton, England. Contact Vanessa Cameron, The Secretary, 17 Belgrave Square, London, SW1X 8PG, United Kingdom; 01-235-2351.

July 6–9, annual conference, Academy of Family Mediators, Portland, Ore. Contact Jim Melamed, Executive Director, AFM, P.O. Box 10501, Eugene, OR 97440; 503-345-1205.

July 10–13, ISAF Second International Congress on Adolescent Psychiatry, Geneva. Contact Mary Staples, Executive Secretary, 24 Green Valley Road, Wallingford, PA 19086; 215-566-1059.

July 12–15, International Conference on Grief and Bereavement in Contemporary Society, London. Contact Derek Nuttall, Director of Cruse, Cruse House, 126 Sheen Road, Richmond, Surrey TW9 1UR, England; 01-940-4818.

July 13–16, annual meeting, Autism Society of America, New Orleans. Contact Ken Laureys, 1234 Massachuetts Ave., N.W., Washington, DC 20005; 202-783-0125.

July 14–17, Second International Congress on Cancer Pain, Rye, N.Y. Contact Mary Callaway, Executive Director, Memorial Sloan-Kettering Cancer Center, P.O. Box 52, 1275 York Ave., New York, NY 10021; 212-794-7456; Telex 649169 MSKCC.

July 15–18, First International Symposium on Group Relations: Contributions to Social and Political Issues, Oxford University, England. Contact Sheila L. Summers, A.K. Rice Institute, P.O. Box 39102, Friendship Station, Washington, DC 20016; 202-363-5443.

July 16–17, 5th Annual Plaza House Conference, Treatment and Prevention of Chemical Dependency in Adolescents: Individual, Family & Community Approaches, Oakland, Calif. Contact Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave., Oakland, CA 94609.

July 19–21, international conference, Initial Effects and Long Term Outcome of Child Abuse and Neglect: Breaking the Cycle, University of Leeds, England. Contact Bell Howe Conferences (CAN), Gothic House, Barker Gate, Nottingham, NG1 1JU, England; 0602-410679.

July 26–30, Fourth World Congress of Victimology, Tuscany, Italy. Contact World Congress, 2333 N. Vernon St., Arlington, VA 22207; 703-536-1750; Telex 9103803091.

July 30–August 4, annual meeting, National Medical Association, Los Angeles. Contact William C. Garrett, Executive Vice-President, 1012 10th St., N.W., Washington, DC 20001; 202-347-1895.

July 31–August 5, annual meeting, International Council on Social Welfare, Berlin. Contact Ingrid Gelinek, Secretary General, Koestergasse 1/29, A-1060 Vienna, Austria.

AUGUST

August 1–6, annual meeting, International Transactional Analysis Association, Rio de Janeiro. Contact Susan Sevilla, Executive Director, 1772 Vallejo St., San Francisco, CA 94122; 415-885-5992.

August 4–11, annual meeting, American Bar Association, Toronto. Contact Thomas H. Gonser, Esq., Executive Director, 750 North Lake Shore Dr., Chicago, IL 60611; 312-988-5130.

August 6–9, annual meeting, National Depressive and Manic Depressive Association, Detroit. Contact Marilyn Weiss, President, Merchandise Mart, Box 3395, Chicago, IL 60654; 312-993-0066.

August 6–12, annual meeting, American Institute of Biological Sciences, Davis, Calif. Contact Dr. Charles M. Chambers, Executive Director, 730 11th St., N.W., Washington, DC 20001-4584; 202-628-1500.

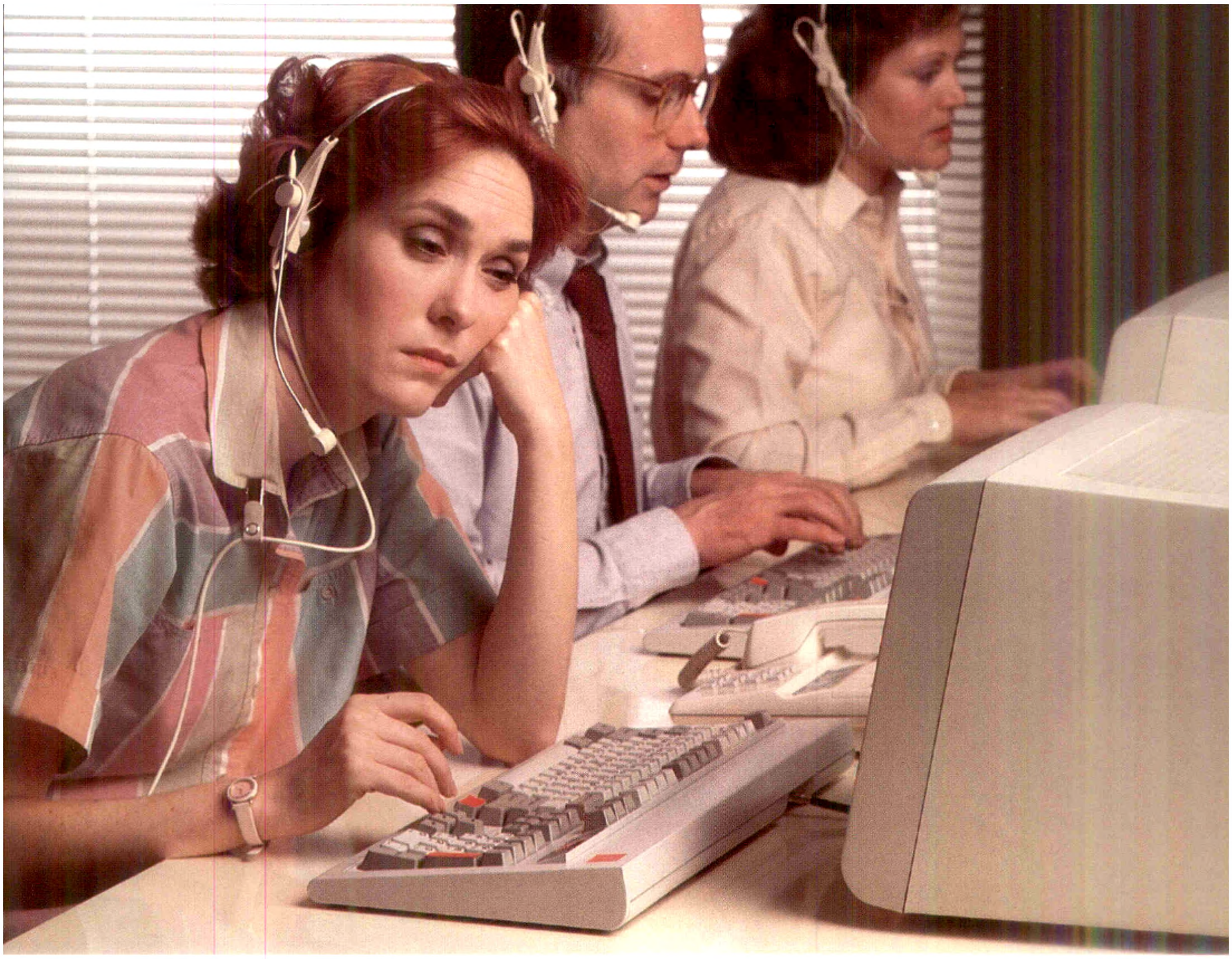
August 8–10, annual meeting, American Hospital Association, New Orleans. Contact Denise Koumiss, 840 North Lake Shore Dr., Chicago, IL 60611; 312-280-6000.

August 12–16, annual meeting, American Psychological Association, Atlanta. Contact Leonard D. Goodstein, Ph.D., Executive Officer, 1200 17th St., N.W., Washington, DC 20036; 202-955-7660.

August 13–19, 11th International Congress of Hypnosis and Psychosomatic Medicine, Leiden/The Hague, The Netherlands. Contact Congress Secretariat, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 071-275294.

August 21–24, XVIth C.I.N.P. Congress, Neurochemical Correlates of Affective Disorders and Their Treatment, Copenhagen. Contact Dr. A. Geisler, Dept. of Pharmacology, University of Copenhagen, 20 Juliane Maries Vej, DK-2100 Copenhagen, Denmark; 1-37-03-75.

(Continued on page A47)



Asleep at the switch.
This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation.
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When patients with depression are being treated with PAMELOR, they're able to keep operating on all circuits.

That's because PAMELOR works as effectively as amitriptyline,[1] yet doesn't keep your patient from working. Daytime sedation is low[2-4]; consequently, patient productivity can remain high.

What's more, PAMELOR has a low incidence of anticholinergic[2,3] and hypotensive[2,3,5-7] side effects. So, for those patients on another antidepressant, a switch to PAMELOR therapy could help across the board.

PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary retention. As with all antidepressants, patients with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time.

For Brief Summary, please see following page.

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PAM 1087-12

PAMELOR®
(nortriptyline HCl)
The active metabolite of amitriptyline

PAMELOR®

(nortriptyline HCl)

The active metabolite of amitriptyline

10 mg/ml 10 mg 25 mg 50 mg 75 mg

All the efficacy of amitriptyline[1] and

- low incidence of anticholinergic side effects[2,3]
- little daytime sedation[2-4]
- low incidence of orthostatic hypotension[2,3,5-7]

References: 1. Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. **2.** Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. **3.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **4.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. **5.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. **6.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **7.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, pares thesias of extremities; incoordination, ataxia, tremors; periphera neuropathy; extrapyramidal symptoms; seizures, alteration in EE patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associ ated sublingual adenitis; blurred vision, disturbance of accommoda tion, mydriasis; constipation, paralytic ileus; urinary retentio delayed micturition, dilation of the urinary tract. *Allergic*—Skin ras petechiae, urticaria, itching, photosensitization (avoid excessiv exposure to sunlight); edema (general or of face and tongue), dru fever, cross-sensitivity with other tricyclic drugs. *Hematologic*— Bone-marrow depression, including agranulocytosis; eosinophili purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomit ing, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in th male, breast enlargement and galactorrhea in the female; increased o decreased libido, impotence; testicular swelling; elevation or depres sion of blood sugar levels; syndrome of inappropriate ADH (anti diuretic hormone) secretion. *Other*—Jaundice (simulatin obstructive), altered liver function; weight gain or loss; perspiratio flushing; urinary frequency, nocturia; drowsiness, dizziness, weak ness, fatigue; headache; parotid swelling; alopecia. *Withdraw Symptoms*—Though these are not indicative of addiction, abru cessation of treatment after prolonged therapy may produce nause headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restless ness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperacti reflexes, tachycardia, ECG evidence of impaired conduction, shoc congestive heart failure, stupor, coma, and CNS stimulation with con vulsions followed by respiratory depression. Deaths have occurre with drugs of this class. No specific antidote is known; general sup portive measures are indicated, with gastric lavage. [PAM-Z13—7/15/8

PAM-1087-12

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Sunday, May 8, 1988
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Breakfast: 8:00 AM - 9:00 AM
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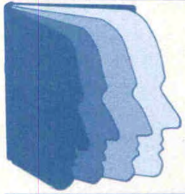

FACES OF DEMENTIA: CURRENT CONCEPTS

Princeton Pharmaceutical Products is pleased to announce a symposium designed to provide insight into the diagnostic, neuropsychiatric, and treatment aspects of dementia. A panel of leading clinicians and investigators will present their views on current concepts in dementia—including Alzheimer's type and AIDS Dementia Complex. Behavioral, psychosocial, and psychopharmacologic approaches to treatment will be examined.

Chairperson: Murray Raskind, MD
Professor, Department of Psychiatry and Behavioral Sciences
University of Washington
Seattle, Washington

Peter Davies, PhD *Professor of Pathology and Neuroscience* *Albert Einstein College of Medicine* *Bronx, New York*	**Neurochemical Studies: An Update on Alzheimer's Disease**
David Ostrow, MD *Associate Professor of Psychiatry* *University of Michigan* *Ann Arbor, Michigan*	**AIDS Dementia: Current Diagnosis and Management**
Peter Rabins, MD *Associate Professor of Psychiatry* *The Johns Hopkins University School of Medicine* *Baltimore, Maryland*	**Psychosocial Aspects of Dementia**
Gary Small, MD *Assistant Professor of Psychiatry* *UCLA Neuropsychiatric Institute* *Los Angeles, California*	**Treatment of Dementia in the Geriatric Patient**
Leon Thal, MD *Associate Professor of Neuroscience* *University of California, San Diego* *San Diego, California*	**Dementia Update: Diagnosis and Neuropsychiatric Aspects**

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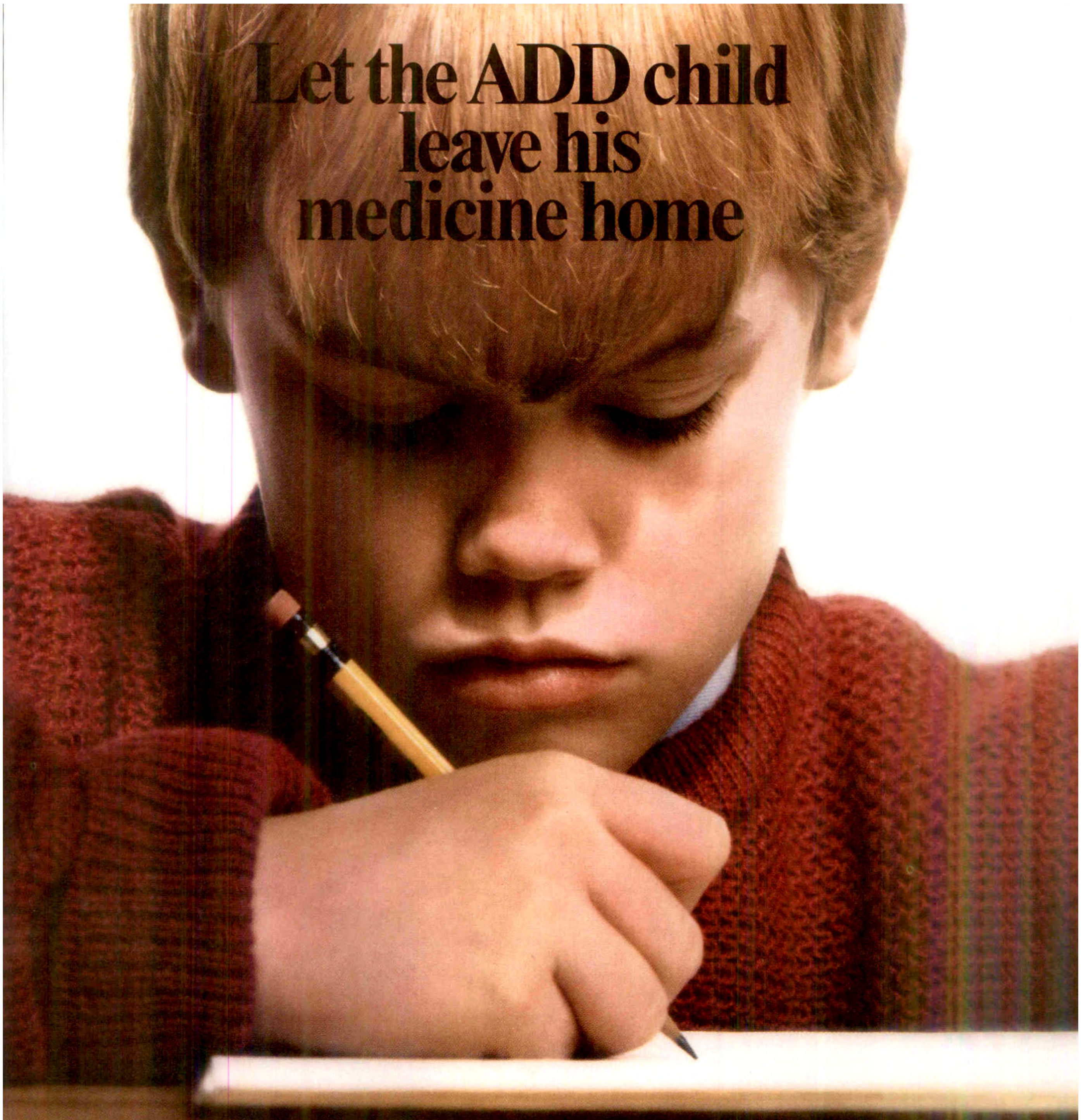


Let the ADD child leave his medicine home

Avoid the problems associated with noon dosing. One 20-mg Ritalin-SR^{C} tablet taken at breakfast provides a therapeutic effect equivalent to a standard 10-mg tablet taken twice a day.[1]

Also available: Regular tablets of 5 mg, 10 mg and 20 mg.

Greater convenience

No medicating at school

Teacher and school nurse not involved

Before prescribing, please consult Brief Summary of Prescribing Information on following page.

Ritalin is indicated as adjunctive therapy to other remedial measures (psychological, educational, social) for ADD children. Drug treatment is not indicated for all children with ADD. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis.

Once-a-day

RITALIN-SR®$^{C_{II}}$

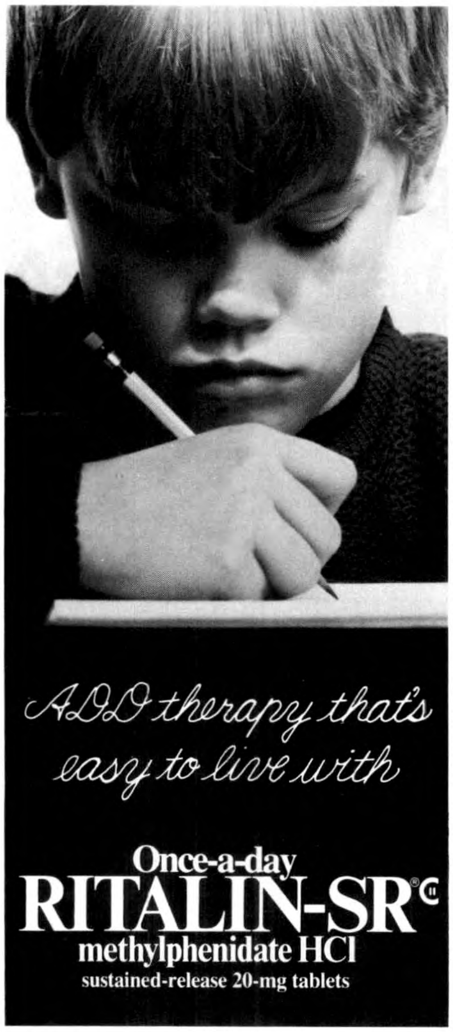
methylphenidate HCl

sustained-release 20-mg tablets

ADD therapy that's easy to live with

174-3185-A

CIBA


ADD therapy that's easy to live with
Once-a-day
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methylphenidate HCl
sustained-release 20-mg tablets

Ritalin® hydrochloride CII
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Ritalin-SR® CII
methylphenidate hydrochloride USP sustained-release tablets

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Ritalin overdosage has not been established.

HOW SUPPLIED

Tablets 5 mg — round, yellow (imprinted CIBA 7)	
Bottles of 100	NDC 0083-0007-30
Bottles of 500	NDC 0083-0007-35
Bottles of 1000	NDC 0083-0007-40
Tablets 10 mg — round, pale green, scored (imprinted CIBA 3)	
Bottles of 100	NDC 0083-0003-30
Bottles of 500	NDC 0083-0003-35
Bottles of 1000	NDC 0083-0003-40
Accu-Pak® Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0083-0003-32
Tablets 20 mg — round, pale yellow, scored (imprinted CIBA 34)	
Bottles of 100	NDC 0083-0034-30
Bottles of 1000	NDC 0083-0034-40

Protect from light.

Dispense in tight, light-resistant container (USP).

SR Tablets 20 mg — round, white, coated (imprinted CIBA 16)	
Bottles of 100	NDC 0083-0016-30

Note: SR Tablets are color-additive free.

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight, light-resistant container (USP).

C85-55 (Rev. 11/85)

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

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1. Whitehouse D, et al: Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *J Clin Psychiatry* 1980;41:282-285.

CIBA

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Printed in U.S.A. (4/87) 174-3185-A

Nippur medical tablet.
Pre-Sargonic 2100 BC.
"World's oldest
prescription."
The University
Museum. (neg #55887)

The First International Conference on Refractory Depression

The University of Pennsylvania
School of Medicine
Depression Research Unit

October 6 and 7, 1988
Four Seasons Hotel
Philadelphia, Penn.

Scientific Agenda

Registration	**Wednesday, October 5, 1988**	
Session I	**Thursday, October 6, 1988**	
Overview of Refractory Depression: Definition, syndromal subtypes, and epidemiology; Neurobiological aspects; Clinical descriptions.	Opening Remarks	Peter Whybrow, MD
	Selectivity of Drugs and Refractory Depression	Stuart A. Montgomery, MD
	The Receptor Sensitivity Hypothesis of Antidepressant Action: Implications for the Treatment of Refractory Depression	Dennis S. Charney, MD
	Systematic Evaluation of 300 Patients with "Treatment Resistant" Depressions: 1975-1987	
	Free Communications	Hagop S. Akiskal, MD
Session II		
Preclinical Aspects: Neurochemistry of refractory depression	The Neurochemistry of Refractory Depression: A Molecular View on Therapy-Resistant Signal Transfer	Fridolin Sulser, MD
	Free Communications	
	Reception and Dinner, Upper Egyptian Gallery of the Archaeological Museum of the University of Pennsylvania	Honorary Speaker to be announced
Session III	**Friday, October 7, 1988**	
Clinical Research: New therapeutic approaches to refractory and resistant depression	Use of Anticonvulsants in Lithium-Resistant, Bipolar Patients	Robert M. Post, MD
	Potentiation of Dopamine in the Treatment of Refractory Depression	William Z. Potter, MD, PhD
	A Trial of ECT is Essential to the Diagnosis of Refractory Depression	Max Fink, MD
	The Treatment of Refractory Depression with Intravenous Infusions of Antidepressants	Paul Kielholz, MD
	Free Communications	

Program Director & Conference Organizer:

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Associate Professor of Psychiatry
Depression Research Unit
Hospital of the University of Pennsylvania

Program Faculty:

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Professor of Psychiatry
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Yale University School of Medicine

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Professor of Psychiatry
University of Basel

Stuart A. Montgomery, MD
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National Institute of Mental Health

William Z. Potter, MD, PhD
Chief, Section on Clinical Pharmacology, LCS
National Institute of Mental Health

Fridolin Sulser, MD
Professor of Pharmacology and Psychiatry
Vanderbilt University School of Medicine

The University of Pennsylvania School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor Continuing Education for Physicians. The University of Pennsylvania School of Medicine designates this continuing medical educational activity for 13.5 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

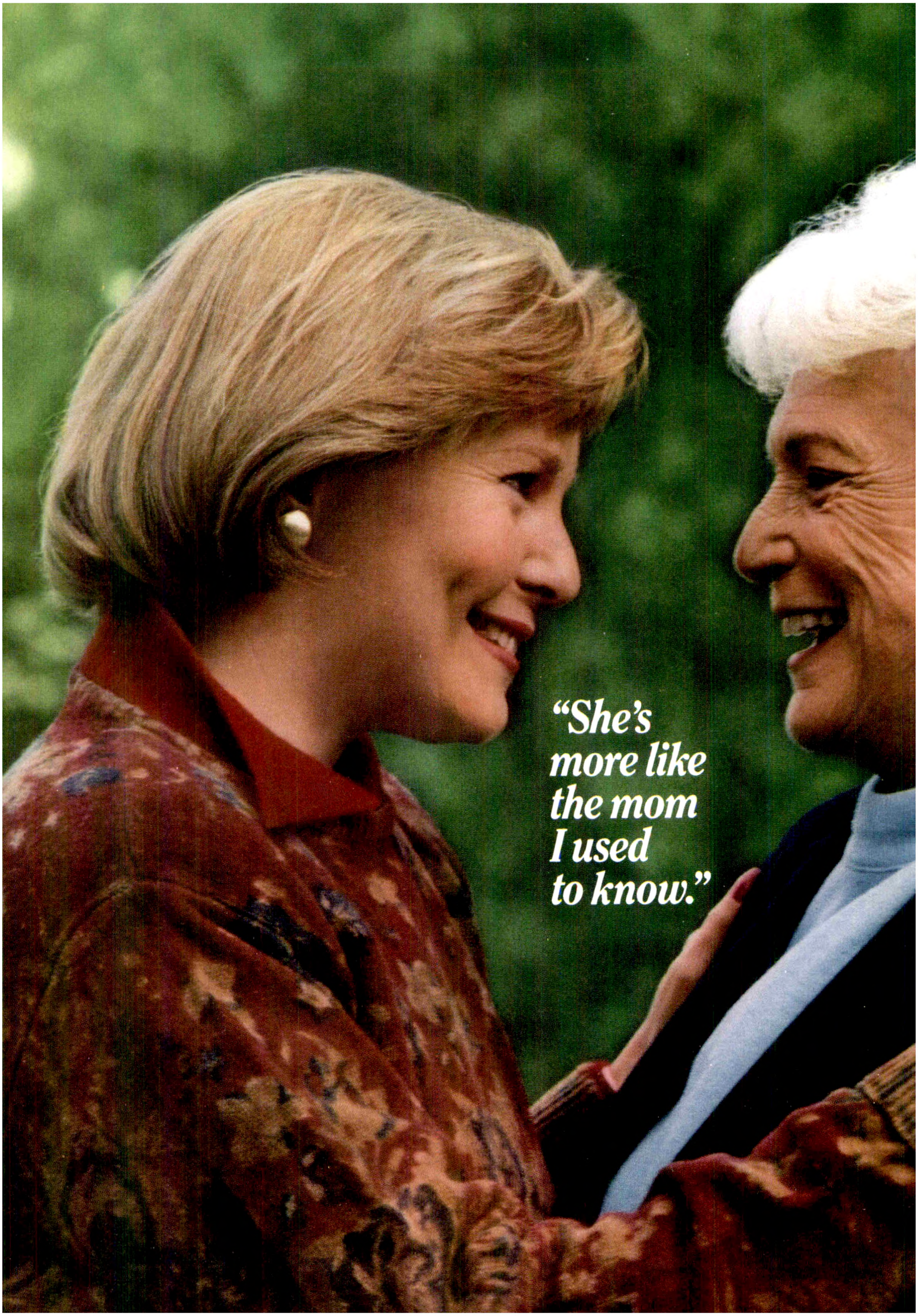
This conference is supported in part by educational grants-in-aid from Merrell Dow Pharmaceuticals Inc., The Jack Warsaw Fund for Research in Biological Psychiatry, and The Department of Psychiatry, School of Medicine, University of Pennsylvania.

Call for Papers

Participants wishing to present a free communication (paper or poster) are invited to submit an abstract before May 30, 1988, to Dr. Jay Amsterdam, Depression Research Unit, Hospital of the University of Pennsylvania, 36th & Spruce Streets, Philadelphia, PA 19104-4283.
Notification of acceptance of abstract for presentation will be mailed by August 1, 1988.

For Further Information

Please contact Dr. Jay Amsterdam, in Philadelphia, at (215) 662-3462, Monday-Friday, 9am-5pm EST; or Ms. Deborah Mullaney, in Los Angeles, at (213) 471-1876, Monday-Friday, between 9am-6pm PST. To write for information, send inquiries to Dr. Jay Amsterdam.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more like
the mom
I used
to know."

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Low-Dose PROLIXIN® (fluphenazine hydrochloride) provides control with a favorable side-effect profile

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A dose of 1.0 mg once a day provides effective maintenance for many geriatric patients.

Low-dose PROLIXIN has a lower incidence of those side effects commonly associated with high-dose, low-potency neuroleptics—anticholinergic effects, sedation, orthostatic hypotension, and ECG changes.*[2-4]

Low-dose PROLIXIN...available in tablets, elixir, and oral concentrate...offering precise dosing for geriatric use.

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favorable side-effect profile

*NOTE: There is an increased risk of extrapyramidal effects with all high-potency neuroleptics.

Please see brief summary on last page of this advertisement.

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PROLIXIN®
Fluphenazine Hydrochloride
INJECTION/TABLETS/ELIXIR/ORAL CONCENTRATE

DESCRIPTION: PROLIXIN Injection (Fluphenazine Hydrochloride Injection USP), **FOR INTRAMUSCULAR USE ONLY,** provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) contains 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. PROLIXIN 2.5, 5, and 10 mg tablets contain FD&C Yellow No.5 (tartrazine). PROLIXIN Elixir (Fluphenazine Hydrochloride Elixir USP) contains 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. PROLIXIN Oral Concentrate (Fluphenazine Hydrochloride Oral Solution USP) contains 5 mg fluphenazine hydrochloride per mL, with 14% alcohol by volume.

CONTRAINDICATIONS: In the presence of established or suspected subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine hydrochloride; cross-sensitivity to phenothiazine derivatives may occur.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop, after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative, effective, less harmful treatments are *not* available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)

This potentially fatal symptom complex has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnostic evaluation is complicated; it is important to identify both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

Management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. Carefully consider the potential reintroduction of drug therapy in patients requiring antipsychotic drug treatment after recovery from NMS since recurrences have been reported. Such patients should be monitored.

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. PROLIXIN Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine hydrochloride cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn. Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine.

ADVERSE REACTIONS: *Central Nervous System:* Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue pro-

References:

1. Raskind MA, Risse SC: Antipsychotic drugs and the elderly. J Clin Psychiatry 47 (suppl to no. 5): 17-22, 1986.
2. Steinhart MJ: Pharmacological considerations in the use of high-potency neuroleptics in elderly patients. Geriatr Med Today 3(2): 65-73, 1984.
3. Salzman C: Treatment of the elderly agitated patient. J Clin Psychiatry 48 (suppl to no. 5): 19-22, 1987.
4. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 221, 222.

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Please see brief summary continuing on adjacent page.

Continued from preceding page.

trusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

Other CNS Effects: Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occur, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage as manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed sudden flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates, and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines.

For full prescribing information, consult package inserts.

HOW SUPPLIED: *Injection*—in multiple-dose vials. *Tablets*—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100, and 500, and in Unimatic® cartons of 100. *Elixir*—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated droppers. *Oral Concentrate*—in bottles of 120 mL with calibrated dropper.

(J4-153A/120B/147B)

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438-504

Issued: March 1988

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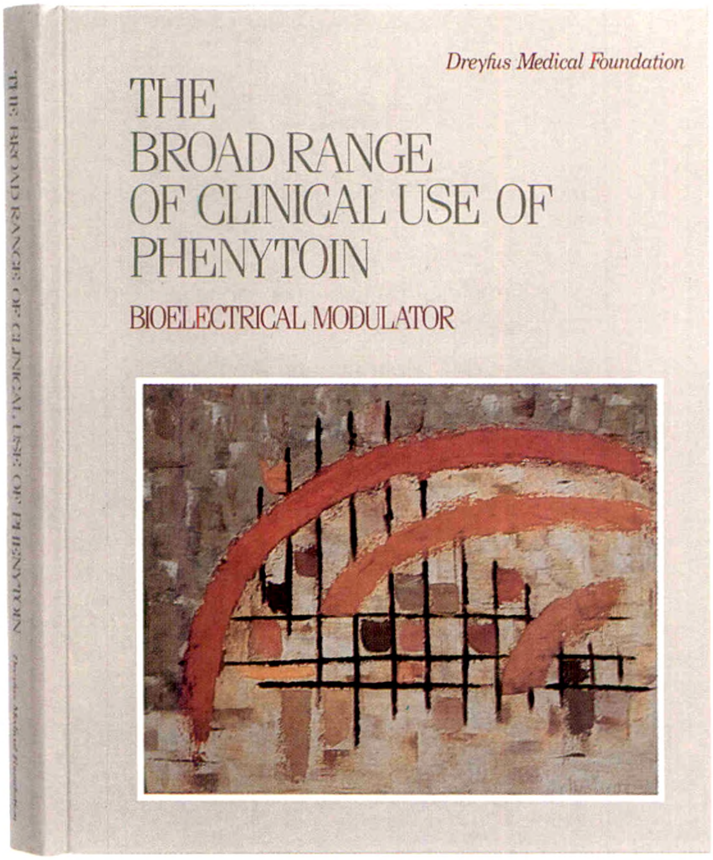
VISIT BOOTH 423 AT THE CONVENTION

A Bibliography and Review of Phenytoin is being sent to all the physicians in the United States.

The purpose of this Bibliography and Review is to put together in one place, for the convenience of the physician and the government, a comprehensive summary of the world medical literature on phenytoin (other than in epilepsy).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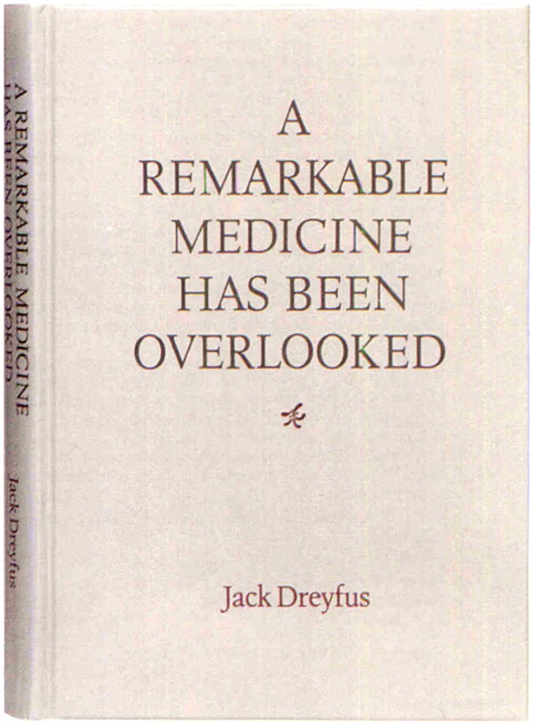

From the Prefatory:

If one looks in the Physician's Desk Reference, one will find that phenytoin's only listing with the FDA is as an anticonvulsant. This is a narrow description of a drug that has been reported by thousands of physicians throughout the world to be useful for over fifty symptoms and disorders.

The lack of understanding of the many clinical uses of phenytoin has tragic consequences. This is not the fault of the FDA. It is not the fault of our physicians. There is a flaw in our system of bringing prescription medicines to the public.*

*The "flaw" is discussed in
A Remarkable Medicine Has Been Overlooked.
This narrative has been republished
to accompany the Bibliography.

The Dreyfus Medical Foundation
is a charitable foundation and has no
financial interest in phenytoin.

*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.
†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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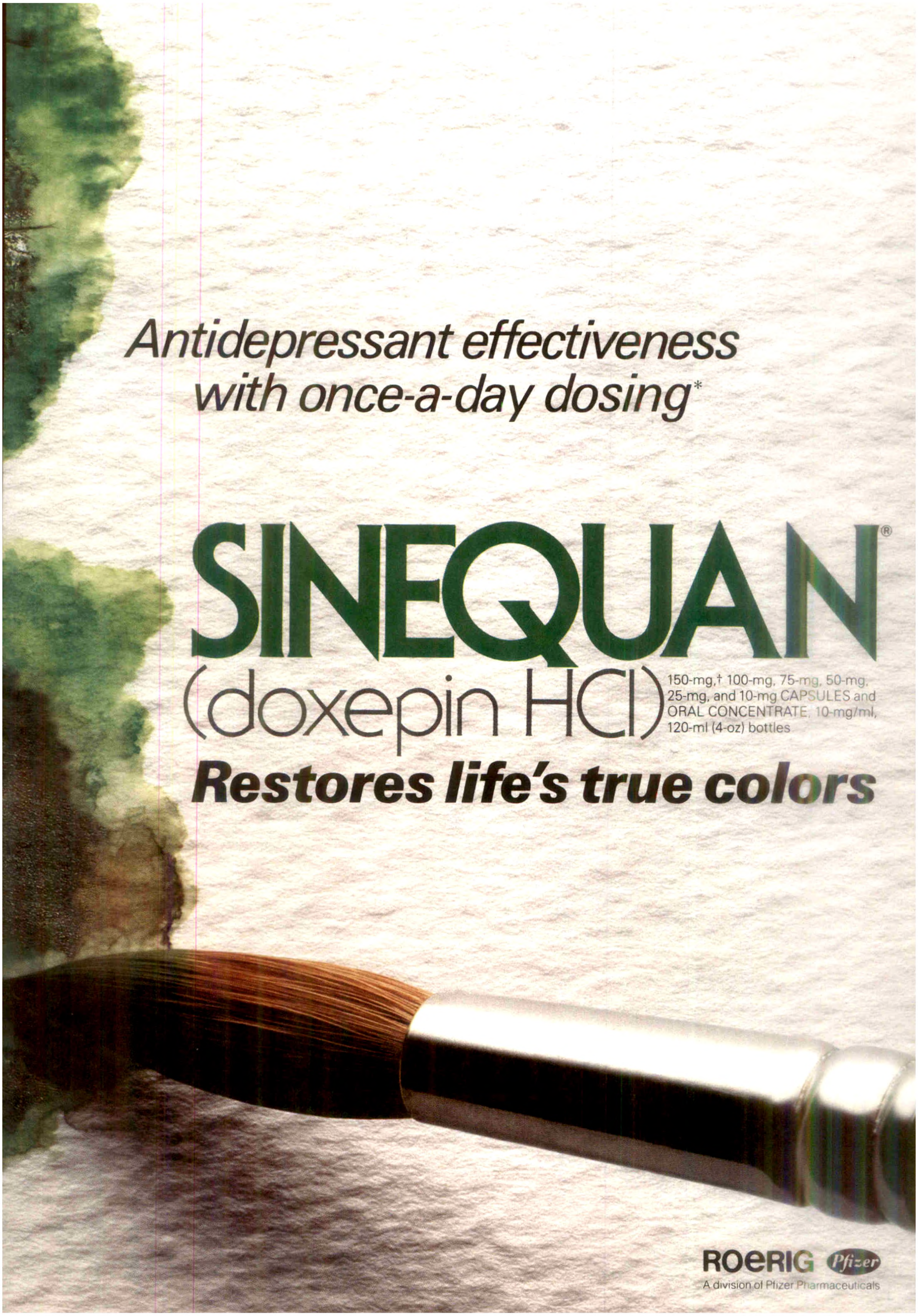

*Antidepressant effectiveness with once-a-day dosing**

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(doxepin HCl) 150-mg,† 100-mg, 75-mg, 50-mg, 25-mg, and 10-mg CAPSULES and ORAL CONCENTRATE, 10-mg/ml, 120-ml (4-oz) bottles

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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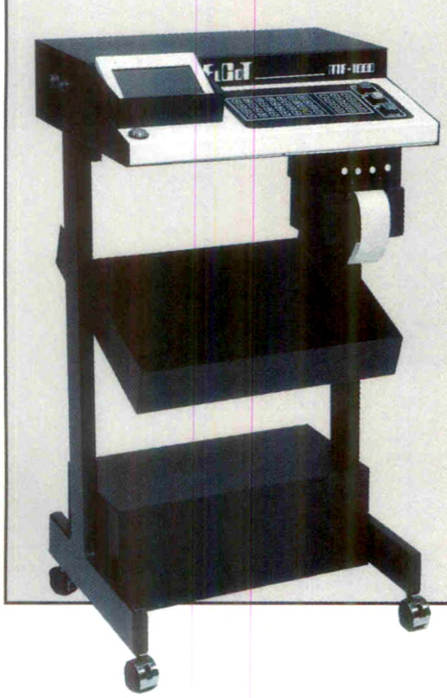

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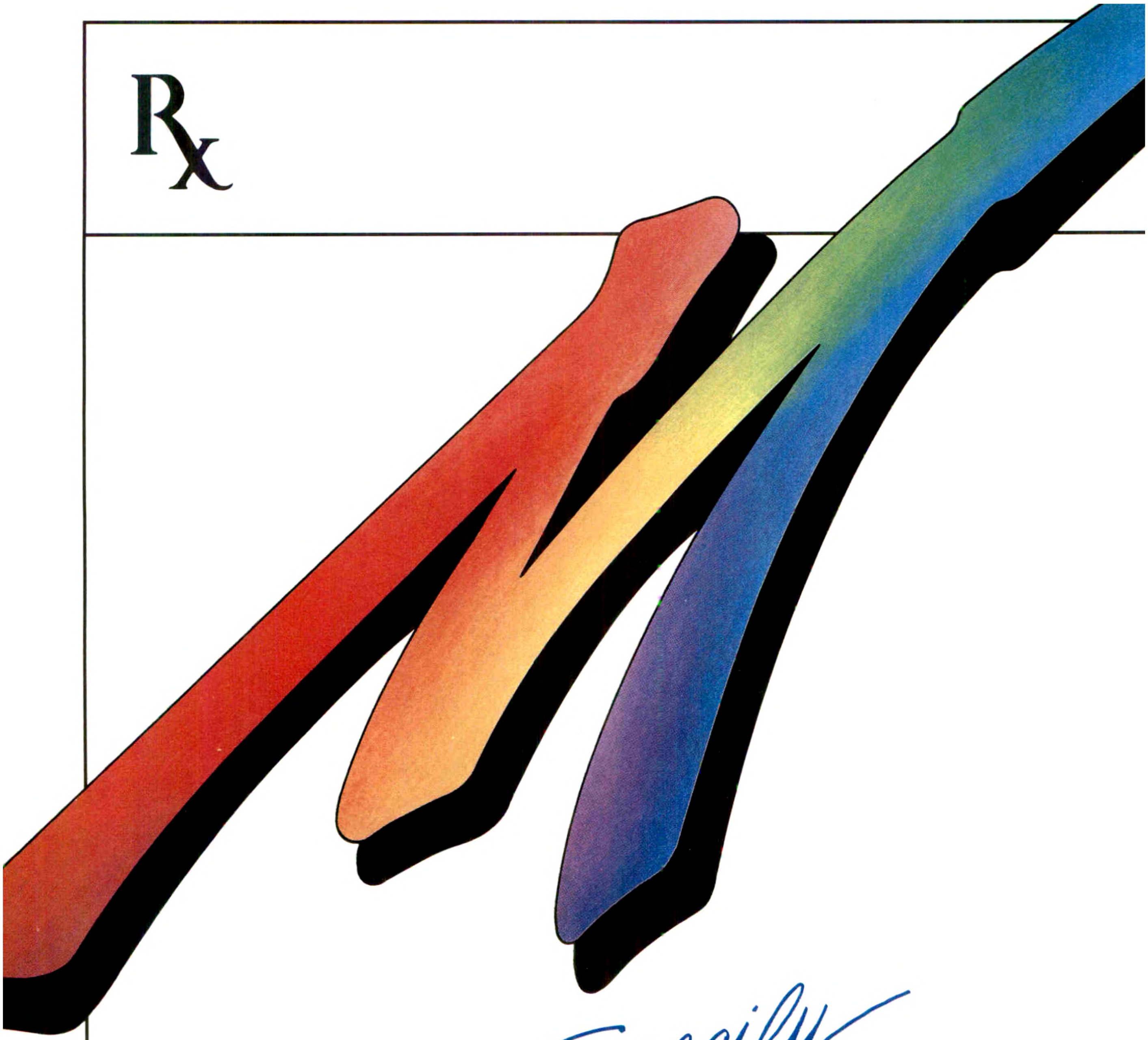

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THE AMERICAN JOURNAL OF PSYCHIATRY

Privatization of Psychiatric Services

Robert A. Dorwart, M.D., M.P.H., and Mark Schlesinger, Ph.D.

The authors provide an overview of privatization, a major trend in mental health policy, focusing in particular on the reasons for and consequences of substantial growth and change in ownership of private psychiatric hospitals; the proportion of all nonfederal psychiatric inpatient beds in private facilities has increased from less than 10% in 1970 to 35% today. It is estimated that between 1970 and 1986, the proportion of total nonfederal psychiatric inpatient beds in the United States that were under corporate for-profit auspices increased from about 1% to 15%. The authors distinguish and examine several aspects of privatization and assess the implications of these changes for psychiatry and for public policy and research.

(Am J Psychiatry 1988; 145:543–553)

Enormous changes in the financing and organization of mental health care have occurred in the past 25 years. They include experiments in prospective payment to hospitals, renewed interest in prepaid health plans, changing patterns in use of mental health services, and growth in the number of privately owned mental health facilities (1–4). The last of these trends has been termed "privatization" and includes both the growing number of private nonprofit and for-profit facilities and the increased purchasing by public authorities of services from private agencies. This paper provides an overview and redefinition of the privatization of mental health care. We seek to identify various dimensions of privatization and discuss some of the reasons for the recent substantial expansion of the proprietary sector in psychiatry. For example, we estimate that between 1970 and 1986 the proportion of nonfederal psychiatric inpatient beds under corporate for-profit auspices increased from roughly 1% to 15%. Thus, this aspect of privatization has become a "megatrend" in mental health economics, the focus of considerable controversy about the relative merits of nonprofit versus for-profit health care,. and a worthy topic for serious debate and research.

Throughout the American health system, there recently has been increasing emphasis on the provision of services through private providers, a process referred to by some as "degovernmentalization" (5, 6). According to Iglehart, American health policies have led to "a reduced federal role, a more market-oriented approach that places an overriding emphasis on price in the decision to purchase care, and more entrepreneurial providers and hospitals, nursing homes, and health care delivery plans" (7, p. 205). Increasingly, some physicians, including psychiatrists, have expressed concern about practicing in the "new business climate" (8, 9).

Privatization in mental health has been slower to develop than in other sectors of health care. Between 80% and 90% of most types of health care establishments in the United States are privately owned. The extent to which these are operated under private nonprofit or for-profit auspices seems to depend largely on characteristics of the service delivered. For services in which physicians do not play a significant role (such as nursing homes, blood banks, and residences for the mentally retarded), the market share of for-profit facilities often exceeds 50%; for services in which physicians play a larger role, the market share of proprietary facilities is generally lower (10). In contrast, until the 1970s more than 90% of psychiatric

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hospital beds in the United States were under public auspices.

Although the growth of privately owned mental health services has occurred more slowly than that of other health services, the dominance of the public sector in mental health services has been diminishing for more than two decades. Starr and others (11–13) have traced the enormous changes in mental health care services that occurred with the advent of more liberal insurance coverage for mental health, the introduction of Medicare and Medicaid programs, deinstitutionalization, the spread of the community mental health center (CMHC), and shortened hospital stays made possible by pharmacotherapy. Privatization in mental health grew in part as these changes increased the profitability of treating the mentally ill and providers accommodated to these developments. It also grew as the result of explicit government decisions to purchase services from private agencies. These decisions were often made by state officials, although they were encouraged by changes in federal law in the late 1960s and early 1970s (5).

In the past, observers of the mental health system have tended to treat the growth of private ownership as a monolithic change. In our assessment, this is a mistake. We believe that there are important differences, in both causes and consequences of growth, between private for-profit and nonprofit ownership, between independent facilities and multifacility corporations, and between private purchase from private providers and public contracting with these same agencies. Others have previously made similar distinctions. Thurow (14), for example, portrays the health care system generally as having three distinct sectors: public, private nonprofit, and private for-profit, each with a corresponding tier or level of care.

In our discussion of the factors encouraging privatization, we will, therefore, distinguish among those which lead to an increase in the aggregate market share of privately owned mental health organizations, those which encourage nonprofit as opposed to for-profit ownership, and those which promote the growth of facilities affiliated with private multihospital systems (sometimes referred to as "corporatization" or industrialization) (15–19). We precede this analysis with a brief review of the growth of privatization in psychiatric hospital services over the past two decades. We conclude with a discussion of the implications of these changes for policy makers and for mental health services research.

GROWTH OF THE PRIVATE PSYCHIATRIC HOSPITAL SECTOR

The proportion of all nongovernment psychiatric inpatient beds in private facilities has increased from 7% in 1970 to 35% in 1987 (20–22) (see table 1). Proprietary ownership (free-standing plus general hospital units) has increased over the same period from about 1% to 15%, while the private, free-standing, nonprofit share changed less. The reduction of state and county mental hospital bed capacity and the concurrent increase in beds in psychiatric units in community general hospitals has also contributed to these changes. Private, nonprofit, general hospital inpatient psychiatry has grown rapidly in the past decade to more than 40,000 beds, or an estimated 20% of the total in 1987, up from 4% in 1970 (4, 23). This pattern of growth and shifting of balance between public and private sectors has also affected patterns of admissions, staffing, and overall expenditures (24).

TABLE 1. Distribution of Beds Among U.S. Proprietary, Private Nonprofit, and State/County Psychiatric Inpatient Care Facilities in 1970, 1980, and 1987[a]

	Percent of Beds		
Type of Facility	1970 (449,000 beds)	1980 (203,000 beds)	1987 (200,000 beds)[b]
Private, free-standing, for-profit	1	4	11
Private, free-standing, nonprofit	2	4	3
Acute care general hospital unit	4	15	21[c]
State and county	93	77	65

[a] Data are from references 20–22.
[b] Data exclude VA and CMHC beds.
[c] According to data from the American Hospital Association, approximately 90% of all beds in discrete psychiatric units in nonfederal, acute care general hospitals are in private hospitals, and roughly 20% of these beds are for-profit.

In 1983, of the 225 private, free-standing, adult psychiatric hospitals in the United States, about 71%, or 160, were owned by proprietary companies (25). Three years later the proprietary hospitals numbered 210, or an increase of about 31%. In addition, 10 of the 40 private psychiatric hospitals for children and adolescents were proprietary, and there was a growing trend for investor ownership of subspecialty programs (26). Between 1980 and 1985, the number of psychiatric units in for-profit community hospitals grew from 50 (with 1,800 beds) to 73 (with 2,300 beds). Furthermore, of the 250 multiservice centers—largely CMHCs with inpatient units—more than 100 were private and 10 of these were proprietary (National Institute of Mental Health [NIMH], unpublished data). Given current growth rates, we estimate that the number of proprietary, free-standing, psychiatric hospitals could exceed 300 by 1988, or triple the number 30 years earlier. Private psychiatric hospitals earned more than $2.5 billion in 1985 or nearly half as much as the direct care cost of treating patients in the much larger segment of state-funded public mental health facilities in the United States. Revenues at private hospitals are expected to grow by up to 50% in the next 5 years (27).

The psychiatric hospital industry has become increasingly dominated by multihospital corporations, which now operate three-fourths of all private psychiatric hospitals. In the mid-1980s each of the four largest psychiatric hospital companies planned to increase the number of hospitals it owned, through new construction, by an average of 10%–20% a year (28, 29). The largest chain in terms of numbers of facilities, Charter Medical, increased by more than 50% between 1984 and 1987 alone; Hospital Corporation of America, which has the largest number of psychiatric beds, grew from 0 to 43 psychiatric facilities in its first 5 years of operation; each company had nearly 5,000 psychiatric beds in 1986 (data from company annual reports, 1984–1987).

The reasons for the growth of private psychiatric services will be discussed in the following material.

SHIFT FROM PUBLIC TO PRIVATE SETTINGS

In a time of public and private pressures to reduce health care costs and institutional capacity, it is somewhat remarkable to observe this growth in private psychiatric hospital care. In our assessment, this growth is attributable in part to the very fact that mental health care in the United States is at a somewhat different evolutionary stage than much of the rest of health care. While general hospital care is marked by the expansion of prospective payment and restrictions on insurance coverage, as well as public and private policies designed to move patients from inpatient to outpatient settings, mental health care has been characterized by continued cost-based reimbursement, stable or expanding insurance coverage, and a perception that public policies may have pushed too far in the quest for deinstitutionalization. These differences in themselves may make mental health care a promising market for investors. But they also reflect three more complex and important ongoing trends that are critical determinants of the privatization of mental health care. These are continued growth of the demand for psychiatric hospital care, ongoing changes in the general health care system, and changes in the goals of state policy makers. We consider each of these in turn.

INCREASED DEMAND FOR INPATIENT PSYCHIATRIC CARE

There is considerable "latent demand" for mental health care. Studies show epidemiologic evidence of an unmet need for psychiatric services, especially among certain groups like the poor, the elderly, and children; we know from recent epidemiologic studies that many people in need of treatment do not receive it (30, 31). The NIMH Epidemiological Catchment Area Program estimated that 29 million people in the United States suffered a mental disorder in 1984; sample interviewing techniques showed that 8% of the population had anxiety disorders, 6% were troubled by affective disorders, and another 6% had substance abuse problems (20, p. 4). It is important to note that fewer than one-fifth of the individuals identified with any mental disorder in a 6-month period used any mental health service from either mental health specialists or general medical physicians.

As a result, factors that increase the ability or willingness to seek mental health care generally can significantly increase the use of inpatient psychiatric care. Five ongoing social and political changes are having just this effect.

First, there has been a significant increase in the number of mental health practitioners. The number of psychiatrists in the United States reportedly increased from 10,600 in 1955 to 33,000 in 1983, with proportionately greater increases in the number of clinical psychologists and social workers (32, 33). During this same period the population of the United States increased by 40%, so that between 1972 and 1982 the number of psychiatrists increased from 120 to 142 per 100,000 population (34). These practitioners serve as gateways to the mental health care system, identifying untreated mental illness and thus increasing all mental health care, including inpatient services.

Second, demand has increased as insurance coverage for mental illness has continued to expand. A majority of states now (in 1988) have some form of mandated insurance coverage and specified benefits for mental health care. While private insurance plans have expanded their mental health benefits as a result, they continue to provide coverage for hospital care in preference to outpatient treatment (35). Consequently, demand for inpatient care has been most encouraged by these state-mandated coverages.

Third, there has been a growth in the overall latent demand for services with the shifting age structure of the American population. The number of persons in the age category 25–44 years increased by nearly 5 million in the first half of the decade 1980–1990 and is expected to increase by nearly that many in the second half (36). This large increase in young adults who are at higher risk for onset of major mental disorders is another reason why the demand for mental health services is currently increasing. The age-adjusted prevalence of psychiatric disorders is an important feature of current and future demands for psychiatric inpatient services, distinguishing mental health from general health care (20).

Fourth, there is growing popular awareness of previously unmet needs among certain groups of Americans. According to the APA Committee on Financing and Marketing, employers now appear to recognize the problem of indirect costs of mental illness related to absenteeism and reduced productivity; awareness has led to the proliferation of employee assistance plans, which have increased nearly fivefold during the past 10 years. Individual employers now issue requests for proposals for mental health services, encouraging responses by the private sector (37). There is also increased concern about untreated mental illness among elder Americans. Both of these trends encourage the growth of inpatient facilities. The employee assistance plans identify conditions that may require inpatient treatment (e.g., substance abuse). Geriatric psychiatry tends to be conducted primarily in institutional settings because Medicare has had such minimal coverage for outpatient care and because many of the most seriously mentally ill elders are residents of long-term care facilities (38).

Finally, demand for psychiatric treatment has grown as such care has become more socially acceptable. While mental illness still carries a stigma, this has diminished over past decades, as the general public becomes more knowledgeable about mental illness and increasingly views "mental illness as an illness like any other" (39, p. 20). Sociologists and others point to the importance of values in the growth and acceptance of health care, especially the concept that health, including mental health, care is a universal right or entitlement. "Mental health services" may be viewed as an expectation or value with several dimensions (40).

One dimension might be called emotional rationality, that is, the wish and expectation to avoid entirely manifestations of psychiatric disorder—to behave "appropriately" or at least to not be "insane." This value, together with a perception of psychiatry as having a solid basis in scientific medicine, has led to greater acceptance of hospital treatment of mental disorder (41). Another dimension of mental health might be called "secular intimacy" and is thought by some observers to explain some of the increasing demand for psychotherapy. By this reasoning, there is a sociopsychological need, formerly met by extended family, religion, or communities, that underlies the economic demand for psychotherapy (42). A related dimension of mental health as a societal value is psychological-mindedness: the value placed on understanding both individual human behaviors and social events in psychological terms. Still another dimension is the "medicalization" of psychiatric disorders, that is, the expectation that psychological distress is appropriately a concern of the medical profession, CMHCs, and health insurers (43). As public acceptance of psychiatric care increases, so does the willingness to seek services for "new" diseases like eating, panic, stress, or addictive disorders. Thus, the value placed on mental health has led to a wish for access to psychiatric and psychological services to obtain help in coping with interpersonal or societal stresses, as well as with major psychiatric or substance abuse disorders (44).

The increased acceptance of treatment as a marketable commodity has helped reduce the social stigma of mental illness. As medicine and mental health care have become more commercialized, there has been an increased willingness among providers to actively market their services. This emphasis on marketing—generally defined as the art and science of creating a demand for goods and services—further induces demand for these services. New configurations and types of services have emerged, including specialized "franchising" and "management contract service" companies in both public and private sectors (45, 46).

The changing epidemiology of diseases also affects the way the community regards psychiatric services; for example, the visibility of problems like teen-age suicides or drug abuse in the schools often stimulates public concern and political pressure for increased consultation, education, and services for special populations. Currently, the federal and state governments, employers, and many insurers are advertising and marketing programs for the treatment of substance abuse. We can see evidence daily of the role of the media and of the professional community in educating the public about the effectiveness of treatment for a wide range of medical and socioemotional problems. There are regular network, station, and cable television shows featuring psychiatrists, psychologists, and others who dispense information and advice about mental health problems; television also broadcasts advertising by hospitals, community agencies, and government about the need and availability of services.

Beliefs about the effectiveness and acceptability of mental health services thus are influenced by social policy, epidemiology, and the media. Such societal and secular trends can, over time, fuel demand in the private sector by fostering a receptive market for development, competition, segmentation, and expansion of mental health services. Increasingly, health care companies are developing along "product lines" that differentially promote various specialized psychiatric services such as child and adolescent services, addictions treatment, and geriatric care.

ONGOING CHANGES IN THE GENERAL HEALTH CARE SYSTEM

The second major trend affecting the psychiatric hospital industry has been an outgrowth of broader changes in the American health care system. Chief among these has been a growing concern about the profitability of community hospitals. Between 1980 and 1985, occupancy rates in community hospitals fell from 75.6% to 64.8% and these rates are continuing to decline (47). Prospective hospital payment using diagnosis-related groups (DRGs) was introduced nationwide under Medicare in 1983, and as of 1986, 11 states had adopted similar systems for their Medicaid programs (48). Although the immediate effects of these changes on hospital profits remain a matter of debate, most observers anticipate that in the long run, profits of hospitals delivering general health care will decline. By comparison, psychiatric services appear to many to be a significantly more profitable market. Consequently, most of the recent increase in general hospital psychiatric units nationally has taken the form of units that are currently exempt from current Medicare prospective payment regulations. The hospitals most likely to institute new units are those in which sagging occupancy rates are driving conversion of medical beds to psychiatric beds.

This shift from general to mental health care has been stimulated by the growth of multifacility health care systems. Many of these systems, and virtually all of the investor-owned variety, were first incorporated in the late 1960s. They grew most rapidly throughout the 1970s. For example, the proportion of beds in system-affiliated hospitals grew from 25% in 1975 to 33% in 1982 (49). By the mid-1980s, however, the growth of all systems among community general hospitals had begun to slow and had only reached 37% by 1985. This slowdown was particularly pronounced among the investor-owned systems, which had acquired all the readily available general hospitals.

The limited potential for expansion of general hospitals encouraged systems to shift their impressive purchasing power into the market for psychiatric services. Systems responded to the same incentives as individual hospitals. When they developed inpatient mental health care they foresaw higher occupancy rates than in general acute care hospitals, less costly operations, less regulation under prospective payment mechanisms, and the ability to transfer difficult and expensive patients to public facilities (50). Because of the systems' ready access to large pools of capital, they were able to respond more extensively to these financial incentives. As a result, by the mid-1980s, about half of the psychiatric specialty hospitals in this country were operated by systems that included both psychiatric and general hospitals. A number of the psychiatric inpatient units in general hospitals are also operated by multifacility corporations, which either manage the units for the hospital or own them under franchise arrangements (46, 51).

CHANGES IN GOVERNMENT MENTAL HEALTH POLICY

A third set of factors fostering the shift of mental health care services from public to private settings involves explicit decisions made by public officials, usually at the state level. Deinstitutionalization, which led over time to a greatly decreased supply of public psychiatric inpatient beds during the 1960s and 1970s, resulted in increased demand for psychiatric services in local community hospitals and in some states encouraged the development of private vendors to provide community support services like crisis, aftercare, and residential treatment (52). During more recent years, when the overall demand for mental health care facilities has been on the rise, government-operated psychiatric institutions have continued to contract for services. Between 1980 and 1985, the number of state and local beds designated for long-term psychiatric care fell by 28%; beds designated for short-term care declined by 15% (47). This has created a market niche for services into which private providers are drawn. In the words of one observer, "many community hospitals are filling the gap as government psychiatric institutions close down and community mental health centers go belly up from lack of federal funding" (53).

The growth of state purchase-of-service contracting in mental health care has also encouraged the expansion of privately owned facilities. Much of this expansion was the explicit intent of state policy makers, who have often judged private providers to have higher quality and lower costs than their government-operated counterparts; most of this contracting has been for services other than inpatient hospital care (5). This may, however, indirectly encourage the growth of private hospitals. When state contracts pay the costs of developing services that are complementary to inpatient treatment—e.g., aftercare or emergency services—they may either increase a hospital's caseload or decrease the ancillary costs associated with operating a psychiatric facility. Either makes private psychiatric hospitals more financially viable.

Finally, the expansion of private mental health has been promoted as states have loosened or eliminated their certificate-of-need requirements for new hospital construction. For example, when Utah recently discontinued its certificate-of-need programs, construction began on eight psychiatric hospitals in Salt Lake City within a 9-month period. Although the executives of most hospital systems have since vowed to avoid such flurries of development—which do little for hospital profits—deregulation still remains a potent stimulus to the industry. Over half the new hospitals being built by one of the nation's largest psychiatric hospital systems were located in states that had dropped certificate-of-need laws (29).

THE BALANCE BETWEEN PRIVATE FOR-PROFIT AND PRIVATE NONPROFIT HOSPITALS

As noted earlier, the privatization of mental health care involves the growth of both for-profit inpatient care, primarily in system-affiliated psychiatric specialty hospitals, and private nonprofit treatment, primarily in psychiatric units of community general hospitals. Given such differences in ownership and institutional setting, it should not be surprising that some of the factors encouraging privatization overall have a greater effect on for-profit providers, others on nonprofit. To have some sense of the future evolution of the mental health delivery system and the likely mix of ownership among providers, it is thus important to identify and discuss these different factors (see table 2).

Both for-profit and private nonprofit institutions benefit financially from the availability of broader insurance coverage. Past experience suggests, however, that for-profit providers will respond more aggressively to these new financial opportunities. Historically, expanding public or private insurance programs to cover additional services has led to a marked increase in the proportion of those services provided under for-profit auspices (9). This has been reflected in mental health care as well. States that have mandated private insurance coverage for inpatient psychiatric care (22 as of 1984) had 43% of their psychiatric

TABLE 2. Factors That Shift the Balance Between Private For-Profit and Private Nonprofit Hospital Expansion

Factor Promoting Privatization	Impact on For-Profit/ Nonprofit Mix
Increased demand for mental health care	
Increased number of practitioners	Promote nonprofit
Increased insurance coverage	Promote for-profit
Increased interest among purchasers (employers, government)	Promote for-profit
Reduced social stigma	Promote both
Changes in general health care system	
Falling occupancy rates in community hospitals	Promote nonprofit
Affiliation of community hospitals with health care systems	Promote for-profit
Changing state policies	
Shrinking of public hospitals	Uncertain and variable
Purchase of service contracts	Promote nonprofit
Loosening or eliminating laws on certificate-of-need for new hospitals	Promote for-profit

hospitals operating under for-profit auspices; states with no mandates had 13% for-profit hospitals (54).

Other demand-increasing factors are likely to have offsetting effects on the ownership mix of private psychiatric hospitals. For the most part, proprietary facilities have marketed themselves primarily to consumers and other purchasers, such as employers. Employers often favor investor-owned health care providers, believing them to be better managed than their private nonprofit counterparts (55). In contrast, nonprofit facilities have traditionally sought to indirectly attract patients by inducing physicians to join their staffs. Many physicians feel more comfortable when they are affiliated with a nonprofit hospital, since they feel that they will be allowed greater clinical discretion in nonprofit settings (8). As a result of these differences in the ways hospitals attract patients, nonprofit hospitals are likely to prosper most in areas with a rapidly expanding supply of physicians and proprietary hospitals in areas in which employee assistance plans and similar contractual arrangements are becoming more common.

Because for-profit treatment most often occurs in system-affiliated specialty hospitals and nonprofit treatment in general hospitals, the ownership mix of inpatient psychiatric care is also shaped by the relative importance of system growth and declining occupancy rates in community hospitals. Hospital systems have grown most rapidly in regions in which population and per capita income are growing rapidly, as well as in those in which hospital profit margins are large (56). One would thus expect that for-profit psychiatric facilities would develop most rapidly in areas with these characteristics. Occupancy rates of general hospitals have been declining fastest in rural areas and the Midwest (21). The private nonprofit share of inpatient psychiatric services is thus likely to be greatest in these areas.

Finally, the ownership mix among private psychiatric hospitals will be directly and indirectly shaped by state policies. Some states, such as New York, continue to prohibit proprietary corporations from operating health care facilities. Other barriers may be less direct. It has been argued that regulations in many states have been hostile to expanding investor ownership and that these regulations have been "captured" by the nonprofit hospitals which they have long regulated. If this is true, then regulations such as certificate-of-need create disproportionately large barriers to entry for investor-owned hospitals. As states abandon their certificate-of-need programs, investor-owned hospitals would benefit the most and would likely grow the most rapidly. This complex problem requires further study.

Conversely, states' purchase-of-service contracting with hospitals traditionally has been limited to nonprofit hospitals. Increased contracting has thus encouraged more nonprofit providers. There is, however, some evidence that these attitudes are changing. Recent surveys of state officials indicate an increased willingness to contract with for-profit agencies for most health and human services (57).

DISCUSSION

In response to the growth patterns we have documented and analyzed, there is both growing interest in and concern about privatization, especially its corporate for-profit form (8, 11). Most of the research to date on the comparative effects of ownership in health care has focused on the general health care sector, but many of the findings from these studies may apply as well to mental health. The general question of what effect the "for-profit enterprise" will have on health care generally has been discussed by the Institute of Medicine (58). Evidence is lacking, however, to assess the impact of privatization in psychiatry on such basic aspects of service delivery as access, quality, costs, and appropriateness of care (4, 58). Also suggesting a need for more research, Goplerud found there to be insufficient evidence to adequately assess the effects of contract management of general hospital psychiatric units by proprietary companies (51).

Although evidence is not complete, there has been no dearth of speculation about the links between ownership form and organizational performance. Table 3 compares many of the common predictions made about for-profit and nonprofit ownership of private psychiatric facilities. In the following section we review studies of mental and general health care facilities that shed light on these claims.

The comparative performance of nonprofit and for-profit privatization of mental health care has been discussed by Levenson, Eisenberg, and others. They focus on the following issues: 1) access to care; 2) quality of care; 3) costs of care; 4) fiduciary responsibility by hospitals, especially in the responsiveness to community needs for care of the chronically mentally ill; 5) the impact on public sector programs; and 6) the

TABLE 3. Common Assumptions and Characteristics in Comparisons of For-Profit and Nonprofit Ownership of Psychiatric Facilities[a]

For-Profit	Nonprofit
Owned and controlled by investors	Owned by nonprofit corporation or trust controlled by volunteer community board of directors
Mission usually stated in terms of growth, efficiency, and quality	Mission often stated in terms of charity, quality, and community service
Access restricted by ability to pay privately	Access not dependent on form of reimbursement but limited by insurance coverage
Quality under pressures of profit motive, defined by consumer preferences	Quality often determined by professional values and standards; treatment sometimes excessive
Increased costs due to higher charges, use of ancillary services, corporate overhead, and need to generate profits	Increased costs due to less efficiency, more professional staff, subsidization of teaching and research
Less responsiveness to community needs	Priority to community service obligations
Treatment of different diagnostic mix of patients (e.g., more affective disorder)	Treatment of sicker and more chronically ill patients
Broader access to capital from equity, retained earnings, debt	Capital sources restricted, coming from contributions, grants, bond debt
Profits subject to corporate taxes	Exempt from federal and state income tax

[a]See also reference 58 (p. 6, table 1.1).

implications for research and postgraduate training (10, 12, 59). We will discuss briefly each of these concerns for which data are available. It is important to keep in mind Levenson's observation that there is tremendous variation in structure, performance, and quality among both private nonprofit and for-profit hospitals and that it is difficult to generalize about either category; some for-profit hospitals may provide extremely high-quality care compared to most nonprofit hospitals, while others may provide extremely poor-quality care (16).

Access

It is feared that privatization will bring increased access to care for insured patients and reduced access for uninsured or inadequately insured ones (10). The limited amount of existing evidence supports this view. Studies show clearly that private ownership is associated with selection of patients on the basis of their ability to pay; reimbursement through government programs accounts for roughly one-quarter of the care in private facilities, in contrast to nearly two-fifths of all expenditures in public facilities (60, 61). Roughly one-third of all patients in public facilities receive care at no charge, whereas less than 1% of private hospital care is without charge; however, the actual amount of free care may be slightly higher—estimated at 3%–4%—but classified as "bad debt."

Differences between for-profit and private nonprofit providers are less pronounced. Nonetheless, nationwide, for-profit psychiatric hospitals offer fewer unprofitable services and are less likely to offer care to patients at reduced charge (5). Statistics from particular states indicate that Medicaid, self-pay, and "no charge" patients are significantly more common in the psychiatric units of nonprofit general hospitals than in units in for-profit general hospitals.

Quality

Quality of care is arguably the most important and most difficult component to measure in mental health care (62). What little data are available suggest that when measured in terms of structural variables, such as staff-patient ratios, there is little difference between for-profit and public settings but that the highest quality care may consistently be available in private, nonprofit facilities (63, 64). Staffing ratios in psychiatric inpatient services differ according to type of ownership and type of setting, that is, free-standing or general hospital unit, with more intensive professional staffing in private nonprofit facilities (4). Beyond mental health care, an Institute of Medicine committee recently found no significant or consistent differences in quality of care between nonprofit and for-profit facilities, but the committee was dissatisfied with the measures used and urged continuous attention to monitoring this aspect of care in both types of facilities (58).

Costs

Nationwide, comparisons of costs among psychiatric units of different ownership are nonexistent. A recent study of costs among California hospitals indicated that although for-profit hospitals had significantly lower, and private nonprofit hospitals significantly higher, costs of direct patient care, total costs did not differ greatly by ownership. In proprietary facilities, cost reductions for patient care in for-profit settings were more than offset by higher costs for administrative services (65).

Several studies of the economic performance of for-profit and nonprofit general hospitals found similar patterns. They have demonstrated that costs of care tended to be highest in public facilities, when measures of service intensity and case mix were controlled; however, there were no consistent differences in costs between proprietary and private nonprofit hospital care (66–68). It appears that care in for-profit facilities is not more efficiently provided and often costs more per day as measured by total charges, since investor-owned facilities have higher "markups" of charges over costs (69). In particular, costs for labor, use of ancillary services, administrative overhead, and capital-related costs may be higher in proprietary facilities. On the other hand, private nonprofit facilities often increased costs because of support for nonreimbursable care and types of services, for research and education, and for intensive professional labor. Clearly, more and better data about psychiatric facilities are needed to explore this issue more completely.

Community Versus Corporate Responsibility

Community hospitals have traditionally been expected to be responsive to local community needs and to provide services considered to be for the general "public good." In exchange for this expectation, they receive tax-exempt status. Hospitals responding to financial incentives to maximize profits may be less likely to respond to local community needs than are tax-exempt institutions. Some observers, however, have questioned the justification of tax-exempt status for nonprofit hospitals by claiming that they give insufficient free care to justify those benefits (70). Others do not believe that hospitals whose managers and board must respond to corporate priorities will be as influenced by local needs, although it is possible that these private facilities will see a mutually beneficial role in an integrated mental health care network or system.

As already noted, privatization today implies in many instances corporate involvement in mental health care delivery. Multihospital and management companies have acquired and constructed free-standing psychiatric hospitals but also have managed nonprofit general hospital units. Under contract they provide programs formerly supplied by public agencies and provide management expertise to practitioners through insurance and group practice arrangements. Relatively little is known about the effect of multihospital system affiliation on mental health care organizations (71). A few large multihospital companies own a majority of proprietary psychiatric facilities. Our review confirms Levenson's assertion that there is wide diversity in these companies of management approaches and styles of practice in delivering mental health care (16, 72). Companies range in management style from centralized to decentralized; some emphasize general psychiatry, while others offer specialized services and a vertically integrated "continuum of care," and they differ in their marketing strategies and in the relative role of psychiatric services in the overall corporate goals. Nonetheless, we anticipate that, in general, system-affiliated facilities will be somewhat less responsive to conditions in the local community than are their independent counterparts.

Impact on Public Sector

State policy makers worry about the impact of privatization on the public sector's services, but they are unsure of its implications. In some states, private sector development is viewed warily. In other states, there are attempts to move the public system toward collaboration with the private sector by obtaining specific services through contracts with private providers or by stimulating growth in the private general hospital sector to meet perceived needs for services, such as acute hospital care. In other states, a major portion of formerly publicly provided services are now offered through contracts with private facilities, arrangements for private management of public facilities, and proposals for coordinated programming between public and private sectors. But the experience with competitive bidding and states' purchase of services by contract has been mixed, leading in some instances to higher costs and apparently lower quality of services (46). Indeed, the impact of privatization on public services is complicated and varies from one state to another. While a problem for private contracting is deciding which delivery systems are best suited for which patients, the larger public policy concern will be how privatization of public services affects access to services. Proponents of privatization point out that while they have been criticized for not giving enough free care, the problem of "uncompensated care" is a major health policy issue that extends beyond mental health care and that solving it will require major changes in health care financing at the federal and state levels.

Teaching and Research

Over the past 30 years, there have been profound changes in the scientific, clinical, organizational, and economic aspects of academic psychiatry. These changes have influenced the nature of our research, the form and content of our training programs, the settings in which we deliver services, and the means by which we support our academic endeavors. As health policy makers focus their attention on cost containment, academic health centers and teaching hospitals are having increasing difficulty in providing patient care while also attempting to achieve training and research objectives. Teaching hospitals have always charged more for their services than comparable nonteaching hospitals in order to support the extra costs of house staff and fellows, more advanced or experimental equipment, and research activities. In addition, many community and municipal teaching hospitals carry a greater burden of free care and treat generally sicker and more chronic—and therefore more costly—patient populations (73). And research funds have failed to keep pace with the cost of maintaining research programs. As a result, many academic institutions are seeking joint ventures with for-profit health corporations in hopes of alleviating current financial strains (59).

Some observers have noted that the fundamental mission of nonprofit teaching hospitals in psychiatry is different from that of proprietary ones and, furthermore, that the training of psychiatric professionals to provide clinical services differs from the education of future scholars, teachers, and researchers (59). History seems to support this view. In California, for example, 40% of the nonprofit hospitals with psychiatric inpatient beds operate approved residency programs; none of the for-profit hospitals offer such programs (65). Others have observed that the affiliation of a teaching hospital department of psychiatry brings with it tangible and direct pressures from corporate management and hospital administrators for accommodation to "business aspects" of hospital care; they also note the considerable financial benefit to the hospital and departments from such an arrangement. There has been to date little effort by hospital companies to support research within the companies; however, there may be a growing awareness of the potential for multisite collaborative work and for the development of benefit-cost and outcome investigations in private hospitals and also of the value of strong academic affiliations. A joint venture contract negotiated by McLean Hospital in Belmont, Mass., represents one attempt to promote academic programs; it provides funds to underwrite the costs of postgraduate training and research as part of an overall affiliation agreement (74). Several other major projects are being developed. Unless adequate safeguards and assurances are devised, there is the risk that problems of conflicting priorities related to a short-term business orientation in proprietary, multihospital facilities, rather than a long-term commitment to research and training needs, eventually will arise in psychiatry.

CONCLUSIONS

We have shown that there is currently under way in the United States a rapid expansion of psychiatric inpatient services, predominantly in the proprietary sector. This emerging emphasis on private services is not surprising because it is consistent with a trend in the larger health care system; federal and state government policies promote the private provision of services, and there is a growing trend toward national multihospital corporations in health care. What is paradoxical about the expansion of psychiatric hospital capacity is that it represents a dramatic departure from recent patterns of care that discouraged hospitalization and runs counter to the prevailing concerns about excessive hospital capacity and costs in the general health care system. Growth and privatization are not haphazard but rather are predictable responses to organizational and financial incentives. There are several major public policy issues resulting from privatization that are likely to be facing psychiatry in the 1990s.

First, the development of a three-tiered or multilevel system of mental health services raises questions about access to services. It appears that the changing system of inpatient psychiatric care is becoming a more complexly stratified system of care than the traditional public-private dichotomy that characterized the last half-century of American psychiatry (75, 76). What must be of immediate concern from the perspective of mental health and public policy is to understand the dynamics of the multitiered system. What are the benefits and costs to society of maintaining separate systems of care? What will be the eventual impact on public systems of care in terms of access, quality, and costs of care in a three-tiered structure? Will competitive forces result in nonprofit hospitals emulating for-profit ones by limiting access to paying patients and, if so, is this desirable or undesirable for psychiatry, patient care, and public policy? A similar set of questions concerns the interrelationship between public and private sectors (77). Surprisingly, this topic has received remarkably little attention in mental health policy research. If the private psychiatric industry continues to follow trends in general health care, this pattern might provide some insights into future developments. Until recently there has been considerable vertical integration in the hospital industry, including psychiatry, but we soon will see movement toward increased horizontal integration.

Second, it is striking in today's health policy climate to see rapid expansion of inpatient services. This suggests that psychiatry will eventually once again have to confront the timeworn questions: How many beds are enough? How many of each kind of service are needed and appropriate? And according to what criteria? With the lapse of certificate-of-need regulation we are possibly headed for an oversupply of private psychiatric beds. If so, what will be the response in a competitive marketplace to unprofitable services? What pressures or mechanisms—professional or regulatory—will be available to monitor appropriateness, or quality of care? As increased numbers of private organizations provide services under contract to government agencies, the problem of coordinating and providing continuity of care becomes crucial. Whatever the benefits of privatization, fragmentation of care is one of the potential pitfalls for some patients.

Third, and related to this point, we foresee an eventual slowing of expansion of psychiatric services and concomitant pressures toward changes in funding mechanisms and better integration of services. Already in response to competitive pressures, a few hospital companies are reporting declining profits and diminished expectations for investment in psychiatric services. At the same time, proprietary ventures in mental health centers, residential treatment centers, and health maintenance organizations are appearing with increasing frequency. Because of concern about rising costs of psychiatric services, prospective payment and capitation plans are being advocated for mental health services by government agencies and private insurers. As these newer forms of organization and financing are developed, it will be important to consider anew the respective responsibilities of the private and public sectors in providing psychiatric services in local areas.

Fourth, further research is needed to study the relationships between ownership forms of hospitals and the extent of integration of hospital-based care to the community and the mental health care system. Traditionally important dimensions of care, such as cost, quality, and access, should be assessed and, in addition, important aspects of psychiatric services specifically related to privatization deserve further attention. On the basis of our review of available evidence, some suggested issues for further study include the effect of ownership form of hospitals on the following: the location of the hospital, patient and service mix, admission and referral patterns, collaborative arrangements with other hospitals and agencies, and interaction with public regulatory agencies. Furthermore, competition from proprietary hospitals may influence the service and patient mix in both public and private nonprofit hospitals and the preferred modes of contracting with public agencies. Finally, the consequences of affiliation with multihospital corporations require further analysis.

In his recent book on the cycles of American history, Schlesinger (78) identified the theme of alternation in social, political, and economic policies of private interest on the one hand and public involvement on the other. Inasmuch as these major shifts affect health and mental health policy and represent not so much a pendulum but rather a spiral of development, he would predict eventually a shift away from privatization toward issues of government responsibility for financing, regulation, and even provision of health and mental health care. Whether the rate of privatization in the future will be slower or faster than in the past, and whether for-profit or nonprofit facilities will play the most important role in this growth, cannot be determined from existing studies. We do not know which of the factors we have discussed has had, or will have, the greatest effect on privatization or ownership mix, nor can we determine with great precision the implications of continued privatization for the cost, quality, and accessibility of mental health care. Nonetheless, it is likely that the current trend toward privatization will mean that the future financing and organizational environment both of public and private provision of services will be more diverse and complex than that of earlier periods of mental health care.

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Lies and Liars: Psychiatric Aspects of Prevarication

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The authors discuss the phenomenon of lying, a common psychic process that has received remarkably little scrutiny. The ubiquity of lying and other forms of deception suggests that they have "normal" aspects, but lying which is persistent or destructive to the quality of a person's life becomes pathological. Lying has many determinants, including developmental, biological, social, and psychodynamic. Antisocial, histrionic, narcissistic, borderline, and compulsive personalities have been associated with lying. The treatment of lying needs to be individualized according to the overall symptom complex in which it is embedded.

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> Lord, Lord, how this world is given to lying!
>
> —Shakespeare: *Henry IV*

Deception, a characteristic of much of the animal kingdom (1), is elevated in the form of lying to a fine art in the human species. Szasz (2) wrote, "It has long been my impression that lying is one of the most significant occurrences, mechanisms, or communications . . . in the field of psychiatry" (p. 272). It is surprising, therefore, that this subject has only seldom been the object of psychiatric or psychological investigation. In this paper we will review our current understanding of the psychological factors associated with lying—including predisposition, psychodynamic issues, characterologic issues, effects of lying, and treatment of the symptom. We hope thereby to stimulate interest in an important but often neglected psychic phenomenon.

Bok (3) summarized the ethical issues related to lying, including lies to one's enemies, paternalistic lies, and lies to the dying. Other areas of deliberate deception that are of concern include false information transmitted between governments as well as between governments and their citizens (4), deception within the economic marketplace (5), and fraud and deceit in the field ostensibly devoted to the pursuit of truth, science itself (6).

Rather than addressing major societal and philosophical issues or the experimental psychology literature in reference to deceit (7), in this review we will focus on internal psychic mechanisms that generate or facilitate lying. We will emphasize the more extreme and pathological forms of lying, recognizing that inferences about more subtle manifestations can be drawn from obvious situations. Although this exposition is not designed to address ethical or moral considerations, the subject is so highly charged that editorial bias is probably inescapable.

DEFINITIONS

Most authors agree that the essential elements of a lie are a consciousness of falsity, the intent to deceive, and a preconceived goal or purpose (1, 3, 8, 9). At the liar's disposal are several modes of prevarication, such as attribution, addition, exaggeration, recombination, and pure fiction (8). The behaviors thus embraced include deceit, cheating, and hypocrisy. Fantasy, rationalization, disavowal, repression, and denial, however, attempt to include even the liar among those deceived. Conscious awareness of falsity is important in distinguishing the liar from the misinformed or the deluded.

Lying readily lends itself to classification, which may attest to its ubiquity and to the varied moral feelings that different lies can engender. "Aggressive" or "defensive" lies (1), "white" lies, and "altruistic" lies (3), for example, convey implicit moral judgments regarding malignity or motivation. Lies can also be differentiated on the basis of pathology, that is, they can be "normal" or "abnormal" ("pathological").

Helene Deutsch (10) wrote that "nearly everyone can recall an occasional minor aberration into the field of pseudology in the course of his truth-loving existence." Essentially everyone has told white lies of a social nature such as how much they enjoyed a party or how well someone looks. In contrast, Selling (11) defined a pathological liar as

> a person having a constellation of symptoms caused by a disease of the total personality characterized psychopathologically by a very definite tendency to tell untruths about

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> matters which perhaps could be easily verified and which untruths may serve no obvious purpose either in the personality of the individual or in the situation which he finds himself.

Davidoff (12) provided a number of additional characteristics of the pathological lie. For instance, such a lie is not determined by situational factors, unconscious motivations predominate, the lie appears to be compulsive and fantastic, and it is destructive to the liar. In general, lying becomes pathological when it interferes with normal development or is destructive to the quality of life of the person involved.

DEVELOPMENTAL, BIOLOGICAL, AND SOCIAL ISSUES

Several issues related to development, brain function, and sociocultural experiences may predispose to prevarication or engagement in the more extreme form of pathological lying, pseudologia fantastica.

Developmental Issues

Developmental issues related to telling the truth have been lucidly described by Goldberg (13). We are indebted to him for the following exposition of developmental issues related to lying.

Concepts of lying and truth telling are inexorably entwined: one cannot exist without the other; one must have knowledge of "the truth" before one can lie (14). A child can neither tell the truth nor lie until his or her cognitive processes have matured. The ego has to be sufficiently developed in the transition from primary to secondary thought processes to make it possible to distinguish between the inner world and the outer world and to test reality (15). Woolf (14) stated that children cannot lie before they are 4 years old because they do not know the truth. After age 5 the concept of lying becomes clearer and there is a greater ability to distinguish external reality from fantasy.

Anna Freud (15) distinguished different forms of childhood liars. Children who regress and engage in infantile forms of wishful thinking in response to intolerable realities (fantasy liars) are different from those who lie for material advantage, to escape from punishment, or from fear of authority (delinquent liars).

Peterson et al. (16) studied how children of different ages and adults evaluated various types of untrue statements. They found that 5-year-olds clearly understood some concepts of lying but tended to confuse these with moral prohibitions. For example, 38% of the 5-year-olds studied defined swearing as lies. Similarly, the 5-year-olds were more inclined to equate guesses with lying than were older children or adults. Younger children were more moralistic than older subjects, and adults were generally more lenient than children in their moral evaluations of false statements.

Several authors (13, 17, 18, 19) have been concerned with the importance of lying as an essential part of psychic development. Separation from the parents, particularly from the mother, is an important developmental task and occurs not only physically but also in terms of psychic structure. At what point do one's own ego boundaries end and another's begin? For the young child the questions are, Am I my own person or am I a part of my mother? Can she read my mind?

Lying becomes an important, perhaps essential mechanism by which the child can test the limits of his or her own ego boundaries in order to define and establish autonomy. If the child tells a lie and the mother acts as if the child is truthful it is evident that the mother cannot control the child's thinking or know the child's thoughts. Thus, lying may be an attempt to differentiate and separate in an effort to establish a distinct and individual identity. Tausk (19), writing in reference to a child's first lies, said, "The striving for the right to have secrets from which the parents are excluded is one of the most powerful factors in the formation of the ego, especially in establishing and carrying out one's own will." Ekstein and Caruth (17) expanded this concept and proposed that genuine intimacy rests on the ability to simultaneously maintain and share secrets.

Kohut (18) offered further proposals regarding the psychic importance of lying by the child. He suggested that the undetected lie of the child revealed a shortcoming in the idealized omniscient parent. However, the lost quality of omniscience is "introjected as a minute aspect of the drive-controlling matrix and as a significant aspect of the all-seeing ego, the super ego." Thus, in addition to being a developmental issue related to separation or autonomy, lying may also play a developmental role in the growth of self-regulation (13).

In adolescence the issues of lying and truth telling are often reactivated. The psychic stresses encountered during adolescence may result in a fragmentation of the self, which in turn leads to a noncohesiveness that may be manifested as lying (13). Both the adolescent and the parents may be in a quandary as to what to communicate to the other. The adolescent may view his or her parents as hypocritical, corrupt, or deceitful. At the same time, the adolescent's struggles over separation often reactivate behaviors such as secrecy and deceit in the effort to become an autonomous person. Adolescents may overreact and indulge in "pathological truth telling" manifested as excessive scrupulosity as they become more familiar with their internal regulatory mechanisms. Goldberg (13) said in reference to adolescence, "No period better demonstrates the idea that lying is as much a part of normal growth and development as is telling the truth."

Biological Issues

Cognitive dysfunction. Several clinical reports of patients manifesting pseudologia fantastica (20–24) indicated concurrent neurological disorders. A number of patients have had seizures, abnormal electroencephalographic findings, and/or a history of head trauma. A disparity between verbal and performance IQ test scores has also been noted in such patients—their verbal scores are significantly higher (20–22).

The most extreme form of this clinical picture is the confabulation seen with Korsakoff's psychosis and other neurological diseases (25, 26). Confabulation does not strictly conform to the definition of lying because there is no conscious willfulness to the deceit, but it has similarities that might prove useful for understanding possible neurophysiological underpinnings of pseudologia fantastica.

Patients with confabulation are highly suggestible and continuously produce verbal material as if it were true. However, as Mercer et al. (27) demonstrated, confabulation is not an all-or-none phenomenon: the veracity of patients' statements is associated with their ability to use information from the environment, including self-correcting clues.

Confabulation is almost always associated with some memory deficits, but the magnitude of the memory problem may be relatively small (25–28). However, a memory deficit is not sufficient in itself to produce confabulation: there must be some associated neurological deficits (25). Stuss et al. (26) found that, in addition to amnesia, frontal lobe dysfunction is a necessary deficit for spontaneous, impulsive confabulation (described as fantastic confabulation by Berlyne [25]). They suggested that the frontal lobes are necessary to critically evaluate and integrate information. Similarly, Bensen et al. (29) found that deficits in the frontal lobes and nondominant hemisphere as well as memory deficits are necessary to produce the syndrome of reduplicative paramnesia (a consistent disorientation to place).

Joseph (28) proposed that when the speech area of the nondominant cerebral hemisphere is unable to access and assimilate all relevant information, other material may be substituted, resulting in confabulation. If the speech area is isolated from other areas of the brain, on which it is dependent for judgment, moral values and analysis, and determination of the relevance of information, it cannot recognize the absurdity of the positions it attempts to advance. Joseph compared confabulation to some forms of self-deception and stated that even in an undamaged brain there are situations in which the speech center, through "gap filling," may provide explanations for behaviors or impulses that seem reasonable, innocuous, and accurate although erroneous.

From the foregoing it can be hypothesized that for some persons there may be an underlying neurophysiological defect predisposing to lying. On reflection, when attention and information are forced on them, these persons can acknowledge the erroneous quality of their statements, but they suffer from a defect in "quality control" of their verbalizations. They fail to examine continuously and self-critically the veracity of their spoken words. Such a defect may be caused by structural or functional deficits in the transmission of information from other parts of the brain to the speech center. This hypothetical explanation is consistent with the phenomenological finding that some patients with pseudologia fantastica have neurological disorders and/or greater verbal than nonverbal skills, findings similar to those in patients with confabulation, "fantastic confabulation," and reduplicative paramnesia (25, 26, 29).

Cognitive style and affect. The concept of cognitive style has been elegantly elucidated by Shapiro (30), who described different modes of thinking. For example, the hysterical cognitive style is dominated by intuition, immediacy, suggestibility, and emotionality; details are not important. It has been observed that persons with a hysterical cognitive style provide personal medical information dramatically but imprecisely and are inconsistent in citing dates and details. This particular style of thinking might result in prevarication because the person pays little attention to accuracy.

The emotional state of persons with a hysterical cognitive style often affects their presentation of both true and false information. This phenomenon has been termed "affective truth," i.e., the truth is defined by what feels right at the moment. The following vignette is a striking clinical example of this phenomenon.

> A histrionic woman who was prone to pseudologia fantastica told a friend who called on the telephone that she had just slashed her wrists after taking an overdose of medication and that the paramedics were rushing to her home. This was blatantly untrue. Later, when the friend angrily confronted her with the lie, the patient replied, "What difference does it make? That's the way I felt at the time."

Another illustration of how affect influences "truth" or falsity is provided by Farber's personal account of an analytic hour during which he emotionally and vividly reported a dramatic childhood event (31). The "memories" were convincing to both the patient and the analyst until reassessment showed that they were to a large extent fabricated.

In contrast to the hysterical cognitive style, the obsessive-compulsive style is one in which there is a preoccupation with details, emotional constriction, and difficulty in assessing the total picture because of a preoccupation with minutiae; i.e., there is difficulty in seeing the forest because of preoccupation with the trees. In providing personal medical information, patients with an obsessive-compulsive cognitive style are often irritatingly precise and repetitious in their efforts to make sure that what they say is accurate.

Social Issues

Child-rearing styles. Whether or not there are differences in "hard wiring" between individuals that account for their propensity to tell the truth, there can be little doubt that parental and cultural factors influence the degree to which children lie. For example, how did the parents respond to the young child's lies—was there severe punishment? Were they ignored? Or were they regarded as cute (32)? Similarly, were the child's fantasies indiscriminately encouraged or severely suppressed or did the parents help the child to recognize the difference between creative fantasy and reality? It is reasonable to assume that the different ways parents respond to their children's prevarications and fantasies extinguish or reinforce certain types of verbal behavior and that the patterns thus established may persist throughout life.

The truthful or lying milieu. Equally important as the response of parents and others to the child's lies and fantasies is the degree to which the child is exposed to lying by others. Are promises made to the child repeatedly broken? Do the parents continually lie to the child? For example, would they tell the child that they are taking him or her to the movies when they are really taking the child to the hospital for a tonsillectomy? Are there many "secrets" in the household? Are certain aspects of the parents' past lives suppressed and/or distorted? Is there hypocrisy in the practice of religious customs or in the observation of laws? Are myths, such as Santa Claus, presented as myths or as fact? The list is almost endless and, to some extent, no family is ever entirely "truthful," but we can readily observe variations among different families. Healy and Healy (21) reported the cases of two individuals for whom pathological lying seemed at least in part due to "contagion from long continued untruthfulness" in their home environment. In one case the patient's marked improvement was attributed to extrication from the lying milieu.

The culture and subculture to which a person belongs may also affect attitudes toward behavior such as lying (33). Short (34) defined a subculture as a pattern of values, norms, and behaviors that have become traditional among occupational and ethnic groups, social classes, persons in closed institutions, and different age cohorts. Miller (35) enumerated six focal concerns or ideals of lower-class culture: trouble, toughness, smartness, excitement, fate, and autonomy. "Smartness" was specifically defined as the ability to "dupe or con" others successfully. Such an outlook extols the virtues of clever deceit and regards it shameful to be so incompetent as to be caught in a lie.

Although skill in lying can be valued in intergroup relations, duplicity is not conducive to group survival and intragroup deception is usually proscribed. Thus, the Junior Outlaws, a Chicago street gang, shares with the Boy Scout oath the common value of trustworthiness (36). A person can be caught between the conflicting values of the larger society and those of his or her subculture. For example, a convict might face a conflict in lying to those who are not prisoners versus lying to other prisoners (37).

Traumatic experiences. The environment in which the child is raised may be so emotionally, physically, or intellectually overwhelming that he or she must use primitive defenses to deal with it. For example, recent hypotheses about the origin of multiple personality disorder (38) revolve around the idea that dissociation is one solution to an overwhelmingly traumatic childhood. Similarly, it can be hypothesized that lying can become a way of concealing and ultimately denying that which cannot be assimilated in other ways. Lying then becomes a form of repression and/or denial. This tentative formulation is consistent with the observations of Fenichel (9) as well as the phenomenological evidence that patients with pseudologia fantastica often report chaotic, inconsistent, and traumatic childhoods (21, 39). In her description of impostors, Greenacre (40) noted one specific form of childhood trauma, death of the father during the future impostor's early childhood.

MOTIVATIONS FOR LYING

The most obvious reason for lying is its external effect: to have an impact on the environment by influencing others. Examples are the exaggerations of the virtues of a product by a salesman to make a sale or the denial of culpability by a miscreant in an effort to avoid punishment. Such instances are situationally determined and readily understandable in terms of motivation. However, as already noted, pathological lying and even "normal" lying often may be repeated even when a useful purpose is not served. Therefore, more subtle explanations for the motivations to lie must be discerned, and we can assume that these are largely unconsciously determined. Several proposed psychodynamic factors that might be anticipated by the consideration of developmental issues already noted will be reviewed separately. It would be reasonable to suspect, of course, that lying is an overdetermined phenomenon in which multiple psychodynamic factors operate concurrently.

Autonomy

As already described, one of the important developmental tasks—separation-individuation—may be associated with lying as the child gradually learns that parents cannot control his or her thinking. Persons who react strongly to control or intrusiveness from others may resort to lying in an effort to maintain a sense of independence. An illustration of this was C.G. Jung's lie to Freud in regard to the latter's persistent questions in reference to a dream (41). Jung deliberately provided inaccurate associations to the dream in question; this deceit allowed for self-delineation and served to prevent regression (13).

Power or Aggression

A basic characteristic of human society is that human relationships and civilization depend on shared information. A person who possesses more information (knowledge) is usually more powerful in controlling both the environment and other persons. One may attempt to gain and keep greater power by maintaining a certain degree of secrecy in regard to information. This phenomenon may be clearly seen in international politics when governments attempt to maintain a high degree of secrecy regarding weapons, economics, and industrial techniques. If information is equated with power, then "misinformation," a term currently in vogue in reference to international politics, is a negative quality that subtracts from power. For example, people who misunderstand other people and/or forces in the environment are far less able to cope with or to control and manipulate their environment and other people. Therefore, lying (the transmission of false information) can be seen as a means of increasing power by deliberately decreasing that of another. Certainly, misinformation limits the rational choices available to the person to whom a lie has been told.

A word of caution is in order in regard to power and lying. Bok (3) noted that power derived from lying is effective only insofar as one is believed; once the liar is recognized as such, his or her information is regarded as suspect. Therefore, the person who becomes known as a liar loses power.

On the basis of the foregoing it is logical to conclude that persons who feel a lack of power would resort to lying in an attempt to gain greater control of their environment. If their initial efforts are successful the behavior can become reinforced. Even though ultimately self-destructive, the behavior is maintained, much as an addiction is, because of the short-term rewards. One of the unconscious motivations of the patient with Munchausen syndrome, who by definition engages in pseudologia fantastica, may be to gain a sense of power by duping physicians (39).

Woolf's description of a 5-year-old boy whose economic circumstances were comfortable but whose father was away in the Army (14) illustrates the use of lying to deny a sense of weakness. The boy feigned poverty in order to successfully beg for money. The successful imposture made him feel triumphant and superior.

Lying is also a way to devalue another person or to project one's own dishonesty in an effort to assert superiority (42). Bursten (43) described this well as the feeling achieved from putting something over on another person. Thus, lying can also be conceptualized as a form of oral aggression or sadism.

Repression or Denial

Lying has been posited by Fenichel (9) to be a mechanism that facilitates repression and/or denial. This process can occur in two ways. An untruth told repetitively over a period of time may become increasingly believable and acceptable as fact to both the person who tells it and the person who is told. (One needs only to look at aggressive advertising campaigns to recognize this effect.) The lie thus aids in disavowal. Fenichel also presented a somewhat more convoluted but plausible explanation as to how lying may assist repression. That is, if a person lies and another person believes what is said, what is known to be untrue seems real and believable. If that which is untrue seems real, then that which seems true may be untrue. Thus, painful memories may be reassessed as untrue or merely imaginary. Marcos's report of a patient who lied continuously during therapy (44) serves to illustrate Fenichel's formulation. This patient's denial of her pervasive sexual problems served the defensive purpose of preventing the emergence of conflictual material related to identification with her mother, who was also sexually dysfunctional.

Lying is by definition a conscious and willful activity, but the need for and the content of the lie may be substantially influenced by unconscious processes. The lie may serve to displace or disguise conscious awareness of conflict. Ironically, however, it can simultaneously highlight it through symbolism (45). Blum's report of the case of a young man who postponed beginning his analysis on the excuse that his mother had just died (46) illustrates this principle. The conscious prevarication was a rationalization for not beginning therapy as scheduled. A year later the young man did begin analysis and confessed his deceit. The content of the lie proved to be a focal point in the therapy, which dealt with the patient's ambivalence toward his mother and unresolved grief over the death of his father during his childhood.

Wish Fulfillment or Regulation of Self-Esteem

Helene Deutsch (10) described pseudologia fantastica as daydreams communicated as reality. She viewed this form of lying as a process that provides partial gratification of the wish along with simultaneous prohibition of the impulse, e.g., the event takes place in fantasy rather than in reality. Similarly, Davidoff (12) noted how the fantasy or the lie involves some sense of gratification, even if only for a short time, for persons who lack the ability to sustain the effort to create or produce accomplishments of their own. This type of lying is more commonly encountered in persons whose aspirations exceed their abilities; they need to see themselves and/or to present themselves to others as more successful than they actually are.

In a similar vein, lying may serve in an effort to regulate self-esteem. Kohut (47) explained that one of the etiologies for lies may be pressure from the grandiose self resulting in the liar ascribing great achievements to himself or herself. Kohut also stated that a person may falsely attribute great achievements and abilities to another person because of the need for an idealized parent image. This false attribution may also be motivated by the need for narcissistic sustenance from an aggrandized self-object or by guilt resulting from surpassing the idealized person (for example, one's father) in accomplishments.

Similar mechanisms have been proposed by others (40, 48, 49) for impostors, who by definition live an ongoing lie. Greenacre (40) interpreted imposture as the acting out of an attempt to achieve a sense of identity and competence. Conrad (48) viewed imposture as "an attempt to avoid exposure; it is a defense against the overwhelming anxiety that would result if the castrated state were exposed." Deutsch (49) stated that impostors strive to eliminate friction between an exaggerated ego ideal and the devaluated, inferior, guilt-laden part of their egos. They behave as if their ego ideals were identical with themselves and expect everyone else to acknowledge this to be the case. Deutsch explained further that a similar mechanism may operate in "normal" personalities, who often pretend to be what they would like to be. One can readily observe persons in day-to-day social relationships who embroider the truth or embellish their achievements to appear more sought after, accomplished, or admirable.

Wish fulfillment of a more infantile type is illustrated by the pseudologia of a nurse with factitious aplastic anemia reported by Ford et al. (50). This woman, who in fact had had a deprived and traumatic childhood, told stories to the effect that she was the pampered daughter of a wealthy man and had been provided with a convertible automobile and other material possessions during her teenage years. Similarly, Frankel (51) reported the case of a man with "hysterical fugue" who compulsively lied and often escaped into flights of fantasy to avoid painful memories and an unpleasant reality.

LYING AND PERSONALITY STRUCTURE

Although lying is by no means typical of only one particular character type, the antisocial, histrionic, narcissistic, borderline, and compulsive personality disorders have traditionally been associated with the symptom of prevarication.

Antisocial Personality Disorder

The association of antisocial personality disorder with lying is partially by definition. According to *DSM-III,* persistent lying is one of the diagnostic characteristics of this disorder. Persons with the disorder have a pattern of repetitive antisocial behavior that violates the rights of others. They also tend to gravitate toward occupations in which certain alterations of the truth are not at all unusual—certain types of sales work, for example. There is also often a close association between antisocial personality disorder and substance abuse disorders, such as alcoholism, and in these disorders denial and repression are often predominant ego mechanisms. The use of alcohol and/or other drugs can be interpreted as an external chemical facilitation of the process of repression. Denial and lying are often seen in persons with substance abuse problems. In fact, their substance abuse is often acknowledged only when they are confronted with overwhelming evidence.

Histrionic Personality Disorder

The relationships of the different personality disorders subsumed under the category of histrionic remain controversial. Kernberg (52) reserved the term "histrionic" for the more regressive personality disorders and noted that persons with such disorders often have a borderline personality organization. Antisocial behavior and pseudologia fantastica may also be present in persons with more severely disordered personalities (52). Guze et al. (53, 54) proposed that the histrionic and antisocial personality disorders are essentially the same entity; the difference is determined primarily by gender.

Although the relationship between the histrionic personality and antisocial behavior is controversial, there is little doubt that prevarication may be part of the histrionic style (55). Wells's description of Scarlett O'Hara (56) from Margaret Mitchell's *Gone With The Wind* (57) is an excellent illustration:

> Her dramatic, attention-seeking, and histrionic behavior indeed went to the extent of lying to achieve her aims. Seeking attention was a way of life to Scarlett, and if she had to exaggerate, act, or even lie, these acts were merely tools, used by her with an artisan's skill.

Another illustration of lying and the histrionic style is Skinner's description of Sarah Bernhardt (58):

> She was indeed a frequent liar. It was all part of her exuberance . . . . She knew the value of a good remark as she knew the value of a good scene. It mattered little if both were make-believe off stage or on, she never stopped acting, and her statements, no matter how exaggerated, sound convincing because she was acting them. (p. xx)

Consistent with this description of Bernhardt is the finding in experimental situations that the lies of subjects who are better actors and who are more extroverted are less likely to be detected (59). Success in lying may serve as reinforcement for the behavior.

Casual lies to the person with histrionic personality disorder are what license is to the poet, and a certain disdain for facts needs to be distinguished from a deliberate and conscious effort to distort them.

Narcissistic Personality Disorder

Narcissistic persons often rearrange the facts of the external world to meet their internal needs (13). Their grandiosity is projected onto their perception of the environment, and their inability to perceive clues and self-correcting information from others facilitates their distortion of reality. Needful of continuous approval from others, they must always present themselves in the most favorable light. This need leads to an exaggeration of their abilities and accomplishments. Feelings of entitlement and the attitude that they do not have to play by the rules governing others often lead to prevarication. Narcissistic persons are often exploitative because they have little concern about how falsehoods may affect others. These characteristics suggest some antisocial features, and Kernberg (42) has stated that persons with antisocial personality disorder have underlying narcissistic or borderline features with severe superego defects.

Bursten (43) suggested that manipulation and narcissism are closely related. His definition of manipulation includes deliberate deception and an exhilarated feeling of putting something over on another person if the deception is successful. The intrapsychic mechanism proposed is that of projection of the narcissist's own feelings of worthlessness onto the victim of the manipulation. The contempt felt toward the victim also serves to bolster the manipulator's fragile narcissistic self-image.

Borderline Personality Disorder

The antisocial, histrionic, and narcissistic personality disorders may all have an underlying borderline structure (42). In addition, the term "borderline personality" has been used to describe many patients who are impostors or who simulate illness (factitious illness or Munchausen syndrome) (60, 61). Different forms of lying, including pseudologia fantastica, are almost always a part of the clinical presentation of patients with factitious disorders (60).

Snyder (62) described four patients with the diagnosis of borderline personality disorder who demonstrated pathological lying. He interpreted the lying as serving several psychological purposes, including enhancement of self-esteem, projection of guilt, and efforts to achieve a sense of superiority over others. He proposed that the lying of borderline persons may represent poor impulse control and an impaired capacity for tolerating frustration. In extreme forms it may become almost indistinguishable from delusions.

Compulsive Personality Disorder

On the surface it would not seem that compulsive persons would be involved in chronic lying. They often pride themselves on their truthfulness and attention to precise details. However, as Dickes (63) pointed out, there is a close relationship between secrecy and lying, and the keeping of secrets can be viewed as compulsive withholding of mental activity. The determinants of this behavior are apparently attempts to protect oneself from overintrusiveness by others. Lying is on a continuum with secrecy in the sense that special and secret information is withheld from others.

The lying of compulsive persons usually is not as malignant as that of those with antisocial, histrionic, narcissistic, or borderline personality disorders; rather, it is more self-protective. For example, one compulsive man in long-term intensive psychotherapy with one of us (C.V.F.) secretly hid from his wife the fact that he was in therapy. He told her a variety of minor lies to explain the time spent away from his office for therapy hours. He was fearful that she would disapprove and forbid him from continuing in therapy, much as she had controlled other aspects of his life.

THE PSYCHOLOGICAL EFFECTS OF LYING

The psychological impact on persons on the receiving end of lies can be devastating. Major life decisions may be based on false information believed to be correct. Lies may also have adverse effects on liars themselves. In this regard Moustakas (64) took the most extreme view. He opined that lying inevitably deters authentic growth and development of the real self: "When we are not honest we are not there. That part of us which if expressed would make us whole is buried and a new, false distorted image replaces the real self." In addition to general effects there may also be more specific effects, dependent on the underlying personality of the liar.

Persons with histrionic personality disorder are often searching desperately for love from another person. Their desire is for closeness, intimacy, and gratification of underlying dependency needs. Their lying, in fact, is often aimed at getting another person involved with them by saying or doing things that will be viewed as ingratiating. It is ironic and tragic that it is the lying itself which often undermines their very wishes and needs. In time the lying becomes more apparent. The very persons from whom they wish love become angry and rejecting. This response may set up a vicious cycle as the person increasingly engages in more lies in an effort to hold onto the love object. Rather than obtaining closeness and intimacy with other persons, the histrionic person drives them away with lies.

The lies of narcissistic persons also frequently serve to undermine basic wishes and needs. Lies may transiently serve as a way to extend their power and to increase their stature in a grandiose fashion. However, inevitably, their power decreases and they are held in progressively lower esteem as their prevarications become known. With rejection and decreased stature, the narcissist experiences "narcissistic injury" and becomes increasingly more depressed and defeated.

The historical example of Sir Cyril Burt is clear in this regard. Burt's expressed purpose in life, "to produce one perfect being for the universe" (65, p. 268), was not realized. He fabricated data and altered the material of others to enhance his own achievements and reputation brazenly and without compunction in his later years. As a result he was forcibly ejected from the psychology department at London University College, where he had been chairman, and lost his association with the *Statistical Journal of the British Psychological Society,* of which he had long been editor. Thus, Burt, who by all accounts was a brilliant man, is remembered for his deceit, exaggerated egotism, unscrupulousness, and carelessness when it came to the truth (65, p. 290).

The effects of lying and secrecy on persons with compulsive personality disorder are more subtle. Basically, the net result is the continuous withdrawal and separation from other persons. Intimacy becomes more difficult because it requires a degree of shared experiences within a setting of trust. For compulsive persons, the fear of intrusion and loss of autonomy may be greater than the wish and desire for closeness and intimacy.

TREATMENT CONSIDERATIONS

Persons rarely, if ever, seek treatment on their own specifically for the symptom of lying. Pathological liars may be coerced into treatment, but the symptom of lying is usually part of a larger symptom complex—in association with narcissistic traits, for example. Two different patients with self-described compulsive lying seen in consultation by one of us (C.V.F.) scheduled return appointments in order to start psychotherapy but failed either to return or to cancel their appointments.

More commonly, the therapist encounters lying as a transient or recurrent phenomenon during psychotherapy. At times these situations may provide rich possibilities for therapeutic interventions. Weinshel (66) reported three cases in which lies provided focal points for the reconstruction of critical traumatic events. His experience with neurotic patients suggested that the lies were similar to "screen" functions—the screen serves as a vehicle for both concealing and exposing an oedipal secret. Similarly, Blum (46) noted that a lie may reveal as much as it conceals.

In reference to lies encountered during psychotherapy, Kohut and Kernberg provided different perspectives consistent with the different styles or techniques of therapy that they advocated (67). Kernberg (42) proposed a vigorous interpretative approach, stating that resolution of the transferential aspects of lying takes precedence over all other material except life-threatening acting out. He viewed this approach as necessary because lying interferes with the psychotherapeutic approach to all other problems. He went on to state that lying indicates a basic hopelessness and an unavailability for an authentic human relationship.

Kohut (68) took a less condemning and more empathetic approach and suggested that the lie, at least in certain instances, may represent the patient's testing assertion of the independent self. Thus, the lie is seen in the context of the needs of the patient rather than necessarily as an attack on the therapist.

Little has been written about the treatment of the pathological liar, but extant recommendations are in general agreement that treatment must be individualized (12, 21, 69, 70). Hall (70) explained, "Because lying is not a simple perversity, rather, born of diverse and even opposite tendencies, a course of treatment that would cure one form would sometimes directly aggravate another." The treatments proposed by different authors combine behavior modification, shaping, environmental interventions, and group and insight-oriented psychotherapy. Davidoff's recommendations for the treatment of different categories of liars (12) would generally fit the histrionic, narcissistic, and compulsive personality styles. For example, he recommended that the person with narcissistic personality disorder receive gentle chiding and that the lies be ignored to the point that the tales grow tiresome. The person with compulsive personality disorder should be encouraged to learn to tolerate imperfections in a supportive environment.

CONCLUSIONS

Lying plays a role in the differentiation of the self during normal development. However, when persistent and compulsive it may result from pathological narcissism reflecting superego deficits, attempts to master feelings of powerlessness, and efforts to regulate self-esteem. Pathological lying may represent core ego deficits.

Although psychodynamic formulations have assisted in our understanding of some aspects of lying, there is a need for more knowledge of the phenomenology of the symptom. For example, we need to ask if child abuse and emotional trauma are predisposing factors. The role of an underlying neurophysiological substrate for some types of lying remains a fascinating but speculative hypothesis that requires further investigation.

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The Idiot Savant: A Review of the Syndrome

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Since it was first described a century ago, the phenomenon of the idiot savant—the juxtaposition of severe mental handicap and prodigious mental ability—has remained unexplained. The author defines the condition, reviews and summarizes the world literature on this topic since the early reports, describes more recent cases, and catalogs and categorizes idiot savant abilities. Theories to explain the condition are reviewed, newer research findings are highlighted, and the far-reaching implications of the idiot savant syndrome for understanding normal brain function, particularly memory, are outlined.

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At the 1964 annual meeting of the American Psychiatric Association, a discussant concluded, "The importance, then, of the Idiot-Savant lies in our inability to explain him; he stands as a landmark of our own ignorance and the phenomenon of the Idiot-Savant exists as a challenge to our capabilities" (1). In the years that have followed, the inability to explain the idiot savant has not lessened, and the challenge to our capabilities remains undiminished. However, no model of brain function, particularly memory, will be complete until it can account for this rare but spectacular condition, with its islands of mental ability in a sea of mental handicap and disability.

Through the past century, since Down's description of this disorder (2), the several hundred idiot savants reported in the world literature have shown remarkable similarities within an exceedingly narrow range of abilities, given the many possible skills in the human repertoire. Why do many idiot savants have the obscure skill of calendar calculating? Why does the triad of retardation, blindness, and musical genius appear with such regularity among them? Why is there a 6:1 male-to-female ratio in this disorder? What accounts for the more common occurrence of the idiot savant among patients with infantile autism than among those with other developmental disabilities?

Most of what we know about health we have learned from the study of disease. Regardless of their particular islands of ability, idiot savants all have in common a phenomenal memory. This dysfunction—albeit spectacular dysfunction—of mind and memory can perhaps, with the kind of careful study and inquiry that has now begun, provide clues to normal mind and memory. This paper reviews the literature on the idiot savant syndrome since the early reports, describes more recent cases, catalogs and categorizes idiot savant abilities, reviews the theories to explain this astonishing condition, and points out the far-reaching implications of the syndrome for understanding normal brain function, particularly memory.

DEFINITION OF THE SYNDROME AND EARLY DESCRIPTIONS

The term "idiot savant" was coined by combining a once accepted classification level of mental retardation—idiot—with the word savant—knowledgeable person—derived from the French word *savoir*, meaning "to know." Its use began a century ago to describe mentally handicapped persons in whom some conspicuous island of ability, skill, or knowledge stood in marked contrast to otherwise very limited intellectual capacity. The term is a misnomer, however, since almost all of the reported cases have occurred in persons with IQs of 40 or above; 25 is the cut-off level for the once popular but now archaic scientific classification of idiot. The idiot savant is not, then, an idiot; nevertheless, the term has endured in spite of its perjorative connotation. Since the condition represents a range of abilities that occur in several conditions, including major mental illness and developmental disability, I prefer the term "savant syndrome," and I will use that term in this paper. Rimland and Hill (3), for the same reasons, used the term "savant" and Charness et al. (4) preferred the term "mono-savant."

The savant syndrome is an exceedingly rare but remarkable condition in which persons with serious mental handicaps, resulting either from developmental disability or from major mental illness, have spectacular areas of mental ability that stand in stark, markedly incongruous contrast to those handicaps. In some of these persons (talented savants), the skills are remarkable simply in contrast to the handicap. In others (prodigious savants), the abilities are not just spectacular in contrast to the handicap; they would be spectacular even if they occurred in normal persons. The condition can be congenital or be acquired by an

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otherwise normal individual following CNS injury or disease. It occurs in males more frequently than in females in an approximate ratio of 6:1. The skills can appear suddenly, without explanation, and can disappear just as suddenly. They occur within a narrow but constant range of human mental functions.

Some well-known psychiatric pioneers observed and commented on savant skills. J. Langdon Down (2) used the term "idiot savants" in his lectures to the Medical Society of London in 1887, describing cases encountered in 30 years of practice at the Earlswood Asylum. Benjamin Rush was fascinated by Thomas Fuller, a Virginia slave who was able to calculate the number of seconds in 70 years, 17 days, and 12 hours "in a minute-and-a-half," taking into account the 17 leap years that would occur in that period (5). Alfred Binet (6) outlined in great detail his observations about two other "lightning calculators" in 1894. Bleuler devoted himself intensively for the last 20 years of his life to the study of mnemonics and, along with Brill (7), was interested in the relationship of memory to lightning calculating, noting that such skills are often accidentally discovered and can suddenly disappear. Others (8–10), beginning with Seguin in 1866, described some early cases.

It was A.F. Tredgold, however, who wrote the first definitive work on this fascinating topic, devoting a chapter to the idiot savant in his 1914 textbook *Mental Deficiency* (amentia) (11). Although more modern and sophisticated theories about the savant have emerged since that time, Tredgold's careful, colorful, and detailed clinical descriptions have never been surpassed. His 20 patients "with special aptitudes which are quite phenomenal, not merely in comparison with aments, but often with the acquirements of ordinary persons" were a catalog and index of the categories of skills possessed by savants which have simply been replicated in the reports in the past 30 years. He described an individual who "possessed an extraordinary memory for data recorded in calendars"; an "imbecile boy of 12 years who would multiply three figures by three figures with lightning rapidity"; an "ament, blind girl affected with rickets, and crippled, who had great musical talents," with the ability to repeat perfectly any song sung or played for her just once; and a cretin with a "marvelous faculty" for drawing cats that were so lifelike and skillfully done that he, Gottfried Mind, acquired fame in Europe and came to be known as "the cat's Raphael." One of his pictures was purchased by King George IV.

Tredgold concluded with a detailed description of the "Genius of Earlswood Asylum," a patient with remarkable skills in drawing, invention, and mechanical dexterity. This patient was congenitally deaf, and Tredgold questioned whether these skills might have been the outgrowth of sensory deprivation in a person of otherwise normal intelligence and whether this might be a case of acquired, rather than congenital, idiot savant syndrome. Nowhere is there a more colorful and succinct description of this remarkable condition than Tredgold's. It remains a psychiatric classic.

SUBSEQUENT SAVANTS AND CATEGORIES OF SKILLS

For the numerous savants described since Tredgold's work, the distinction between talented savants and prodigious savants has not been consistently made. If one restricts the term "savant" to persons in the latter category, the cases remain few, probably fewer than 100. The skills of the savant fall into remarkably consistent categories in all of those descriptions. Mechanical ability is one such talent (9, 11–14).

Lightning calculating and mathematical ability are talents possessed by many savants, including Critchley's "brain athlete" (15), a "blind, intractably destructive imbecile who was able to give cubits rapidly and solve algebraic problems with no knowledge of the rudiments of geometry." Scripture (16) distinguished between auditory and visual calculators, and Smith (5) outlined interesting cases including Jedediah Buxton, Henri Mandeux, and Thomas Fuller. Brill (7) described a case of acquired savant syndrome and discussed the topic of "memory without consciousness," which so characterizes savants regardless of their particular individual skills.

Exceptional mnemonic skills are also frequent (14, 15, 17). Tredgold (11) recounted Forbes Winslow's case of a patient who could remember the day every person had been buried in the parish for 35 years, with age of the deceased and the mourners at the funeral. He described also an "imbecile" who could repeat verbatim the contents of a newspaper he had just read and another patient who could repeat backward what he had just read. Barr (18) reported a 22-year-old woman with a mental age of 5 who was able to recall the dates of every visit that had been made to her and the names of each of the visitors, extending back for years. George, one of a set of twins who are calendar calculators, remembers the weather for every day of his adult life (19). Byrd (20) described an early case in 1920, and Jones (21) reviewed the topic in a later article.

Artistic talents have been possessed by some savants who have become quite famous, such as Gottfried Mind of an earlier time (22) and Richard Wawro of the present day (23). Kiyoshi Yamashita, a graphic genius with an IQ of 68, was known as the "van Gogh of Japan" (24, 25). Nadia, a child with extraordinary drawing ability, which she later lost, seemingly as a trade-off for language development, was very carefully studied by Selfe (26). Numerous other artists have been mentioned through the years (27–30).

Calendar calculating is commonly reported. Some writers maintain that such skill is not calculating at all but, rather, visual imagery—a "mnemonic tapestry"—wherein the savant sees an endless scroll or landscape of the calendar from which he or she simply chooses the correct answer (19). The identical twin calculators have this ability covering a span of 8,000 years; they are also capable of "swapping 20-figure prime numbers" and factoring complex numbers and have a possibly unlimited digit span (1, 19, 31). Hill (32) concluded that this talent reflects a special ability to concentrate for long periods of time. O'Connor and Hermelin (33, 34) concluded, from study of eight savant calendar calculators, that rote memory alone is inadequate to explain this skill and that some rule-based strategies are used by all savants.

Musical skills are also common; Charness et al. (4) reviewed 15 such cases. Of particular interest is the triad of blindness, musical genius, and retardation, which occurred in six of those 15 cases. In addition, "Blind Tom" was a well-known savant with a very limited IQ who played Mozart works on the piano at age 4 and could play back flawlessly any piece whatever, no matter the complexity (35). He could repeat a discourse of any length in any language without the loss of a syllable. Once tested with two compositions of 13 and 20 pages, he repeated them without error. The 35-year-old blind male savant with whom I have worked has that same prodigious musical and memory skill (36), as does another 30-year-old blind female savant with whom I have been working recently. In these two cases and in almost all the others reported, the blindness is associated with retrolental fibroplasia, raising interesting questions, as outlined by Rimland (37), about the role of hyperoxia as a possible causative factor in autism and in these cases.

Viscott (38) provided a psychodynamic study of a very skilled female musical savant who was humming complex operatic arias at the age of 6 months. Minoque (39) presented a case of "secondary mental deficiency" following meningitis, which left the patient's unusual musical ability intact, suggesting that musical ability can develop apart from general intelligence. Other reports (40–42) have described savants with musical aptitude limited in almost every instance to playing the piano and singing or humming, usually with perfect pitch and perfect recall. Sloboda et al. (43) reported a musical savant in careful detail, comparing the savant's memorization, note by note, to that of a professional pianist in one tonal and one atonal composition. They concluded that the savant's memorization skills, though impressive, were confined to tonal music and were structure-based.

Other savant skills include map memorizing, visual measurement, and extrasensory perception (44, 45); unusual sensory discrimination, such as enhanced sense of touch and smell (1, 8, 11); writing and composition based on memorization (14, 17, 46); and perfect appreciation of past or passing time without knowledge of a clock face (2, 45).

Skills often occur in some combination in the same savant. In Rimland's 119 patients, music and memory were the most commonly seen abilities and they were often linked (44), as they were also in Duckett's study of 25 savants (47).

PREVALENCE OF THE DISORDER

There has been no well-designed study of the prevalence of the savant syndrome. The most often quoted rate is 0.06%, or about one per 2,000 in an institutionalized mentally retarded population (48). Hill derived this figure from a 1975 canvass of 300 facilities in 39 states in which information was requested on any idiot savants in those programs. Fifty-four savants were reported in 23 facilities with a total population of 90,000 patients.

Rimland (44) found "special abilities," as reported by parents, in 531 autistic patients out of a population of 5,400 cases. His prevalence rate of 9.8% among autistic children, like Hill's rate of 0.06% in a developmentally disabled population, was not based on a definition of savant skills and did not differentiate between talented and prodigious savants.

The consistently high male-to-female ratio among savants suggests that the disorder is sex-linked. Of 103 individuals classified as savants in 63 publications, 89 were male and 14 were female, giving a 6:1 ratio (22). Interestingly, this same preponderance is found in infantile autism, in which the prevalence of savant skills is also high (49). Rimland (44) noted a 3.25:1 male-to-female ratio in the 119 autistic individuals with savant skills that he studied. Since savant skills are frequent in infantile autism, where the male-to-female ratio is also high, this could account, in part, for the sex ratio in the savant syndrome overall.

THEORIES TO EXPLAIN THE SAVANT

No single theory, as yet, can explain the savant syndrome. The theories are nearly as individual and as numerous as the case reports. The explanations do fall into some general categories, however.

Eidetic Imagery

Eidetic imagery is an intense, positively colored visual image, aroused and maintained by scanning an object or stimulus, that persists for a long period of time, generally at least 40 seconds (50). The term is also often used for a related but separate phenomenon called "visual image memory," which is the ability to scan quickly and store, for later recall, vast amounts of detailed information (photographic memory). The terms for these two processes are often used interchangeably, yet debate continues about whether these two phenomena are different only quantitatively or whether real qualitative differences exist between them (51). Duckett (47) defined them carefully and separated them as variables in her study of savants and a matched group of retarded subjects.

Roberts (52) described the case of a patient with unusually vivid eidetic imagery and provided some experimental support for this hypothesis. Several investigators (1, 19) have described the twin savant calculators as having this unusual visual imagery. LaFontaine (53) used that explanation for one case but also concluded that such a special sense could not account for cases in which the calculations extended into the future, for which no calendars were available. Jaensch and Menhel (54) suggested the eidetic imagery explanation in their case also.

While eidetic imagery may be present in some savants, it is not a universal explanation. Duckett (47) systematically tested 25 savants for the presence of eidetic imagery, and LaFontaine (53) likewise tested her five subjects; both concluded that while some savants did show such skills, it was not a uniform finding in all cases. Two other investigations (32, 55), in specific testing of individual subjects, found no evidence of eidetic imagery. The case reported by Rubin and Monaghan (56) of a blind calendar calculator with very limited Braille skills casts doubt on eidetic imagery as a universal explanation. The fact that eidetic imagery can be viewed as a marker of brain damage when it persists beyond childhood or adolescence (50) and the fact that such imagery is sometimes seen in certain types of brain injury (palinopsia) (57) raise the question whether eidetic imagery, when it is present in the savant, is an indicator of some type of brain damage or dysfunction rather than a unique savant characteristic.

Inherited Skills

Rife and Snyder (58) argued that mentally retarded persons with special abilities have received coincidentally two sets of hereditary factors, one for retardation and one for special ability. They studied 33 such patients, paying special attention to any family history of the talent the savant demonstrated. They concluded that special abilities appeared as separately inherited characteristics in the handicapped person as well as in relatives with normal intelligence, that these abilities were not merely gained from training and experience by either the normal or the handicapped relatives, and that it was only a coincidence when the savant inherited both a special ability and a handicap. These authors stated forcefully that their genetic findings refuted any behavioral explanation for the savant. Jones (21) was concerned with genetic factors also, but saw those in conjunction with other factors as well. Brill (7) pointed to unconscious memory and inheritance of acquired characteristics as the primary factors in the savant syndrome.

Goddard (9) proposed that these skills were genetically determined and that if the individuals had not been mentally retarded, they would have been geniuses within the area of their skills. Duckett (47) found special skills in some of the relatives of the 25 savants she studied. Rimland (44) also commented on the tendency of savant skills to run in families, but LaFontaine (53) found only one family member with special skills among the 23 relatives of five carefully studied savants.

Like eidetic imagery, hereditary factors are seen in some, but not all, savants. Thus, while they may be a contributing factor, they are not a universal explanation.

Sensory Deprivation and Social Isolation

Another possible explanation is that sensory deprivation, resulting either from social isolation or from defective sensory input channels, leads to boredom, which sensitizes the savant to minute changes in the environment and leads to the development of bizarre or trivial preoccupations, concentration, or rituals such as memorizing obscure facts and calendar calculating. Some authors (11, 38, 56) have pointed to social isolation as one cause of this intense concentration. Others have pointed to a more biologically mediated, true sensory deprivation resulting from blindness, deafness, or other altered sensory pathways. Rimland (44) postulated that in the autistic savant, attention is pathologically locked at the indistractible, superintense end of the concentration scale. This is a form of sensory deprivation predicated on inability to broaden sensory input; the savant deals only with minute details of great specificity and has an inability to broaden scope or perceive stimuli in anything but an extremely narrow range.

Hoffman (59) suggested that "the elimination or reduction of outer interfering stimuli to a minimum level" is of major importance. He pointed out that individuals in extreme isolation sometimes develop feats of mental calculation or rote memory as a way of adapting to that environment, and he theorized that the savant does this as well in the development of special skills. Nurcombe and Parker (60) also implicated sensory deprivation in the etiology of the savant syndrome.

Social or psychological deprivation may be applicable in some instances, but many savants have histories of very stimulating environments with a great deal of personal attention. Similarly, while some blind, deaf, or otherwise sensorily impaired individuals develop savant skills, most do not. The undistractibility and narrow concentration band of the savant is more likely a symptom or marker of the condition than the cause of the disorder.

Concrete Thinking and Impaired Ability to Think Abstractly

Some authors think that the defect in savants is an inability to think abstractly, which produces reliance on concrete thinking. Organic brain disease has been postulated by some (8, 54) as the cause of this impaired conceptual ability. Others (52) have suggested psychogenic causes, including familial and environmental factors, for the impairment. Nurcombe and Parker (60) described the central defect as an "inability to think abstractly together with the retention of functionally isolated 'islands' of concrete ability" and pointed to maternal and sensory deprivation, along with organic brain damage, as causes of this defect.

This particular theory was most thoroughly explored by Scheerer et al. (55) in a detailed 5-year study of an 11-year-old savant with skills in music, calendar calculating, and verbal retention. They concluded that when an individual is handicapped in abstraction yet endowed with skills in a particular field of performance, there is a linking of subnormal intelligence and abnormal channelization of the aspects of the particular environment. This linking is compensatory in nature: savants channel all their energies into the only outlet available for actualization—concrete mechanisms of expression—and this accounts for their tremendous motivation within the very circumscribed areas in which they can function. In formal neuropsychological testing for this trait in a savant, Steel et al. (61) found impaired ability in verbal abstraction and a high degree of concrete verbal memory. Luszki (62) also documented the highly concrete skills and impaired abstract abilities on the WAIS of the deaf retarded savant he studied.

This finding of excessive concreteness in thinking and impaired ability in abstraction appears again and again in research reports on savants. However, like inability to broaden sensory input, it is a description of the savant rather than an explanation.

Compensation and Reinforcement

Some researchers (55, 59, 63) have postulated that the savant uses compensatory skills, such as deliberate memorization, to offset generalized skills or as a coping mechanism. Praise rewards the savant for an unusual skill and meets needs for self-esteem (53); the skill compensates for inferiority feelings (21), serves as a defense for intellectual defects (24), aids in the direct search for relationships with others (60), or is used to gain parental approval and love (38). Jones (21) suggested that the skills are a search for stimulation, along with unbreakable habits and repetition compulsion, and Fauville (64) concluded that constant absorption in special skills leads to neglect of other behaviors. Duckett (47) and Hoffman (59) both highlighted the fame that savants receive in institutional settings, which gives them immense social reinforcement.

While these factors no doubt exist in the savant, they cannot by themselves account for the condition. These same dynamics of compensation for defect or search for areas of competence so as to obtain self-esteem or praise are forces in all developmentally disabled persons, yet most do not achieve the performance level of the savant. Consequently, there must be specific and unique factors aside from these commonly held psychological dynamics that separate the savant from the rest of the mentally handicapped.

Right Brain/Left Brain Localization and Other Organic Explanations

A number of investigators have suggested that the typical savant skills tend to involve abilities associated with right hemisphere functions. Brink (13) proposed these organic factors to explain the savant—specifically, left brain damage that produces retardation, with compensatory development of the right hemisphere. He presented the case of a normal 9-year-old boy who suffered a gunshot wound to the left hemisphere, leaving him deaf, mute, and paralyzed on the right side. Following that injury, an unusual savantlike mechanical skill emerged, presumably from the undamaged right hemisphere. Tanguay pointed out that the skills seen most often in autistic savants tend to be those associated with right hemisphere function, and the skills most lacking tend to be associated with the left hemisphere (P.E. Tanguay, paper presented at the UCLA Conference on Cerebral Dominance, Los Angeles, Jan. 5, 1973). Expanding on this, Rimland (44) reported on specialization of hemisphere function in the autistic savant, highlighting the simultaneous nature of right brain activities and the sequential nature of left brain activities. The savant seems to rely on simultaneous, high-fidelity imagery and other right brain functions. In the case of Nadia (26), the suggestion was made that development of language represented a substitution of left brain skills for what had been right brain savant abilities.

Horwitz et al. (1) alluded to a "specialized computer-like mechanism" in the brain of the savant, and others as well have inferred some idiosyncratic brain circuitry as an explanation for the savant. However, biological studies of savants are sparse; there have been four post-mortem brain dissections. Down's patient (2) showed only "two well-marked and distinct soft commissures" different from the ordinary brain, and Ireland's patient (65) had a rather small brain with a somewhat enlarged cerebellum. Sano (10) gave an exquisitely detailed sulcus-by-sulcus description of Pullen's brain, which showed marked arteriosclerosis and enlargement of the ventricles; arrested development of the central, temporal, and frontal lobes with preservation of the occipital lobes; and a less complex convolutional pattern on the left than on the right in the frontal areas. Sano felt that these findings accounted for the unusual visual and artistic skills of the patient. Steinkopff (66) described post-mortem findings in a male calendar-calculating and musical savant with symptomatic right-side epilepsy; there was no macroscopic abnormality, but there were microscopic changes in the temporal area in the fourth and fifth cortical layers.

EEG findings were normal in the twin calendar calculators reported by Horwitz et al. (1), but there were higher amounts of REM sleep than anticipated (67). Steinkopff (66), who gave his calendar-calculator savant an EEG while the savant was calculating, noted that there was cortical arousal.

The literature contains reference to one CAT scan performed on a savant (61). The findings on the scan and on an EEG were normal, as were urine screens for amino acids, reducing substances, and heavy metals and the results of chromosome analysis of a buccal smear. A detailed neuropsychological test battery report showed preservation of the capacity to reason, with the use of mathematical but not linguistic symbols, and implicated frontal lobe regions as areas of specific difficulty, with better preserved right posterior function. With respect to brain injury and the savant, Bakwin and Bakwin (68), in speaking of the twin calendar calculators, made the pertinent observation, "It seems hardly likely that both of them could have sustained an injury to the brain in exactly the same area." They argued, rather, for a genetic or behavioral explanation of the twins' special ability.

In summary, to date, there is no single, universal finding that can explain the savant syndrome in all cases. Two studies (47, 53) that particularly searched for an explanation across categories of savants found no single etiology. The behavior of savants is complex and difficult to comprehend, and despite the fact that it clearly does exist, this behavior remains unexplained in individuals and in the aggregate. The search for an explanation continues.

MEMORY AND THE SAVANT

Superior memory is a trait many savants share. For some, this is in fact their special skill. Tredgold (11) noted, "In a considerable proportion of idiot-savants, the gift is one of memory in some form or other, and of this, many interesting and remarkable examples have been cited." Down (2) commented on outstanding memory in his cases, using the interesting term "verbal adhesion" to describe this distinctive kind of memory. The early cases reported by Seguin (8), Barr (18), and Byrd (20) pointed to "precocious and phenomenal memory" as savant skills. Jones' case of K (21) provided very detailed and startling examples of prodigious memory. Study after study has mentioned the memory skills of savants. Holstein, in discussing the paper by Horwitz et al. (1), summed it up quite well: "It is interesting to speculate that perhaps the phenomenon of a type of memory which Idiot-Savants have represents memory which in some fashion has developed separately from general intellectual ability as a part of the personality. This notion is not unusual since paranoid schizophrenics have an exquisite memory, and in a general way they incorporate their memory ability into their personality. At any rate, the qualities of memory that George and Charles and the others exhibit are apparently not associated with any aspects of mental functioning associated with their intelligence of which they are impoverished."

Spitz and LaFontaine (69) found that eight savants had digit spans which were significantly superior to the digit spans of a control group of educable mentally retarded subjects. This finding is in contrast to studies by Byrd (20) and Mogridge and Healy (70), which found spans of three to four digits. Hill (32) felt that rote memory was an important factor in the savant, as did Horwitz et al. (1). LaFontaine (53) tested five savants on the Wechsler scales and found that the highest scores for all subjects were on memory items that presumably measure short-term memory; on those scales the memory quotient was higher than the IQ. Steel's autistic idiot savant subject (61) scored in the 97th percentile on the Wechsler memory scale, and the high WAIS verbal IQ was due to "concrete verbal memory." In Duckett's study of 25 savants and matched retarded control subjects (47), she found that savants were clearly superior in symbolic and semantic memory, without differences in figural memory, and that "the superior memory span skills of idiot savants have little if any relationship with global intelligence or length of institutionalization." In contrasting the "savants whose talents could be explained by memory" with those who had talents in art, music, crafts, and mechanics, and comparing them to their control subjects, Duckett found that "the significant differences in memory were accounted for by the memory experts, calendar calculators, and those idiot savants whose skills were in the area of academics."

The question of memory versus mathematical ability in calendar calculating has been of special interest. Some writers (1, 21, 54) have postulated an eidetic imagery memory as the mechanism. Others (71) have pointed to a specialized mechanical memory that is not calculation at all, but an operation of systematic memory of different dates of each year, through which the savants deduce the first day of the month, following rules which are fixed in their memory. Testing for the role of memory in calendar calculating, O'Connor and Hermelin (33, 34) concluded that such a task was a combination of memory and use of calendar regulations, even though the subjects were unable to verbalize the rules and strategies of the calendar and its regularities. Critchley (15) agreed, but gave memory special importance when he stated "Memory is more important than reckoning." A study of one savant with exceptional musical memory (43) showed that the subject had a memory resembling that of prodigies with high IQs—structure-based and structure-preserving—which supports the view that general intelligence is not a prerequisite for structure-based skill and suggests that human intellect is a set of partially independent intelligences, each of which can develop, at least to some extent, without the others.

In commenting on prodigious memory as the hallmark of the savant, Goodman (72) noted that what stands out remarkably is the savant's long-term memory, a capacity which may be due to failure in the swift metabolism of short-term memory. Thus, she, along with Bruner (73), raised the interesting possibility that the defect in the savant may be a failure to forget rather than an enhanced ability to store. Rosen (74), in his detailed study of two adult calendar calculators, also commented on the prodigious long-term memory of the two subjects.

Unique, at times prodigious, memory function, retained in the face of other severe defects, is frequently although not universally seen in savants. This finding points to a promising area of further study, since it occurs with considerable regularity, is cited often by independent investigators, and in some instances cuts across categories of skill.

NEW CASES, NEW FINDINGS, AND NEW DIRECTIONS IN RESEARCH

"As to how and why . . . we can only conjecture," concluded Tredgold in 1914 (11). We conjecture still in trying to fit the savant's remarkable juxtaposition of ability and disability into present-day psychological and neuropsychological constructs. But new cases, new findings, and new techniques provide an opportunity to take savants from a "gee whiz" status to serious study with sizable samples, matched control subjects, and techniques that assess not just brain structure but brain function as well.

New Cases

As interest in the savant accelerates, new cases come to attention. One is that of a 30-year-old sculptor who has remarkable talent with crystalline clay and who has achieved considerable acclaim in art circles nationally; his ability emerged following injury (75). His IQ is 40; his skill has progressed from earlier, more primitive figures to life-size bronze works, always of animals. I have had the opportunity to work with him and his family, and his skill is truly prodigious.

Miller (76, 77) has reported his work with a 7-year-old multiply handicapped boy with remarkable musical talent whose abilities surfaced at age 3. When the boy was tested at age 5 on the Callier-Azusa scale, his social development was at the 12-month level and his daily living skills were at the 40-month level. His speech was limited to single words or simple phrases, and his vision was severely impaired, yet with no formal training, the child has a large piano repertoire of modern and classical pieces, has perfect pitch, and can duplicate, as well as provide improvisations on, complex pieces after a single hearing. Miller noted, after careful testing, that the remarkable memory shown by this boy is not literal repetition but incorporates, as well, impressive sensitivity to rules governing composition and suggests an implicit knowledge of structural rules not limited to those learned from earlier experiences.

Charness et al. (4) described a 36-year-old blind, hemiplegic man with demonstrated left hemisphere damage who has a highly skilled piano talent, a large repertoire of a variety of music, perfect pitch, and an impressive knowledge of the "vocabulary" of music without formal training. His musical memory is not literal or eidetic but shows knowledge of musical structure and some cognitive coding of musical information. He can transpose keys, improvise, and imitate, yet he functions at a level of severe mental retardation. Left hemisphere damage points to right brain dominance. Charness et al. concluded that "intense practice together with an intact neurological substrate for coding a musical symbol system is sufficient to explain J.L.'s performance."

Sloboda et al. (43) presented the case of a 21-year-old male savant with an IQ of 61 who had an exceptional musical memory. He had perfect pitch, a vast repertoire of piano music, the ability to improvise, and rapid memory—structure-based as opposed to pure mimicry. Some access to the "rules of music," again with no formal training, was evident.

The 35-year-old male savant (75) that I have examined shows the same exceptional musical memory, perfect pitch, and a seemingly endless and varied musical repertoire. He can reproduce lengthy piano compositions after a single hearing. He is blind due to retrolental fibroplasia, has atonic diplegia, and has an IQ of 58. His speech is limited to simple phrases and echolalia. Neuropsychological testing shows short-term memory in the normal range but poor performance on other scales. There is severely impaired ability in nonverbal abstraction. A CAT scan shows left hemisphere abnormality with a relatively large low-density area of atrophy in the left frontal lobe and associated focal cortical atrophy in the left anterior parietal area. There is also a lesser degree of atrophy in the left posterior parietal area and a minor degree of atrophy in the occipital lobes bilaterally.

Hermelin and O'Connor (78) have been able to identify as many as 12 new savants, which provides opportunity not just for individual study but for work with matched control groups of other handicapped individuals as well as normal subjects to compare findings with those of the earlier studies (79) that had larger samples. The rarity of savants has prevented this until now, but with newly enhanced communication among investigators and the media uncovering new cases previously unknown to researchers, sizable samples can be gathered; the research questions are exciting and promising (80, 81).

New Findings

Geschwind and Galaburda (82) have reported some interesting new findings on cerebral lateralization that may provide answers to some questions about the savant. Citing a wide variety of animal and human studies, they have pointed out that the left hemisphere normally develops later than the right and is subjected to prenatal influences for a longer period of time. One of those influences is a male-related factor, perhaps circulating testosterone, that can slow growth and impair neuronal migration and assembly in the more vulnerable left brain, with an actual enlargement and shift of dominance to the right brain. This produces anomalous dominance favoring talents associated with right brain skills, the kind of skills seen in the savant, and is associated with the same marked male-to-female sex ratio in savants as is seen in dyslexia, delayed speech, autism, stuttering, and hyperactivity. It also accounts for a higher frequency of left-handedness in males in general. A "pathology of superiority" is postulated, with compensatory growth in some portions of the brain (right brain) as a result of either poorer development or actual injury in left brain areas. These hormonal effects on brain structure, particularly the cortex, offer considerable promise in explaining the predominance of males with savant syndrome and the predominance of right brain skills. While a compensatory shift to right brain dominance is not a new idea entirely, earlier theories that implicated brain injury, as opposed to these hormonal influences, could not explain why injury would occur so much more commonly in males; this finding accounts for that difference.

Evidence in support of such left brain dysfunction in the savant comes from a study by Hauser et al. (83) in which they found pneumoencephalographic abnormalities involving the left temporal lobe and dilatation of the left temporal horn of the left lateral ventricle in 15 of 17 autistic patients. Four of these 17 autistic patients had savant skills in music or mechanical areas, and the generally high prevalence of savant skills in autism makes this a relevant finding. Hauser et al. concluded that in these patients there was a deficiency of brain substance in the left cerebral hemisphere, a distinct flattening of the normal hippocampal contour on the left, some associated minor disease on the right, and the "taking over" of some motor and language functions by the right hemisphere because of disease on the left. Interestingly, there was an unusual frequency of left-handedness in this series of patients. The authors speculated that this fairly consistent abnormality was caused by ischemic-hypoxic injury, since the medial temporal structures are especially sensitive to hypoxia, and the number of instances of prenatal or perinatal complications in their series of patients, and in others, was significantly high. The CAT scan documentation of left hemisphere abnormality in the savant I have been working with and the demonstrated left hemisphere abnormality in the savant reported by Charness et al. (4) lend further support to such an etiologic framework, at least in these individuals.

Earlier concepts of distinct and isolated right brain/left brain task specialization have been replaced by more sophisticated models. Restak (84) pointed out that division of the hemispheres' functions into symbolic-conceptual (left) and nonsymbolic, directly perceived (right) avoids oversimplification and is a more accurate representation of that dichotomy. Savant skills are usually of a more concrete, nonsymbolic, directly perceived type (right brain), although hemisphere specialization is not absolute and some cross-representation does exist.

Savant memory is also characteristically direct and nonsymbolic, with rather automatic, nonemotional functioning within a very narrow area. Such unconscious memory—memory without reckoning—suggests, perhaps, the use of what Mishkin and Petri (85) referred to as a noncognitive "habit" formation system, rather than a cognitive "memory" system, when they proposed two different neural circuits for these different types of memory. Similarly, the importance of the hippocampus and amygdala in differential memory functions—the hippocampus for simple recall and the amygdala for cataloguing and providing emotional tone to memory—suggests disturbances in that circuitry in savants, given the usual type of memory function that they demonstrate. Rimland and Fein (45) suggested that perhaps deficiencies in the functioning of the amygdala produce an overreliance on the hippocampus in memory function and retrieval, producing the characteristic episodic, high-fidelity, stream-of-consciousness, supranormal memory that savants exhibit. Hyperfunction of the hippocampus could account as well for the low distractibility and the defects in attention proposed by Rimland (44) as central to the etiology of early infantile autism, in which savant skills appear so frequently.

In support of these hypotheses, Bauman and Kemper (86) found demonstrable abnormalities in the hippocampus, selected areas of the amygdala, the cerebellum, and other areas of the forebrain in a careful histoanatomic post-mortem comparison of the brain of a 25-year-old autistic patient with a control specimen. They concluded that such pathology occurred early in development (prenatally) and included destruction of neurons, which is consistent with the theory, mentioned earlier, of a prenatal shift to the right brain, with neuron migration and reassembly. Bauman and Kemper concluded, "Although defects in memory have been little studied in autism, they may well underlie the pronounced difficulties in social interaction, language function, and learning that characterize these patients."

These newer findings provide a framework for answering, in a beginning sense, the major question savants present: How do they do it? At this point, it appears that the answer lies in a disruption of typical left hemisphere functions resulting from prenatal influences, sometimes sex-linked, or prenatal or subsequent injury, which leads to a compensatory migration of neurons and dominance of right hemisphere function. This abnormality is coupled with idiosyncratic hippocampal/amygdala/forebrain circuitry, probably arising from those same influences and injuries, which produces the savant's characteristic cluster of symptoms, capabilities, defects, and unique memory.

The predilection for simultaneous, high-fidelity, nonsymbolic, literal skills and functions is reflected in the cortical migration and rededication and in the unique neural circuitry of the memory. In talented savants, concreteness and impaired ability to think abstractly are locked in a very narrow band but, nevertheless, with constant repetition and practice can produce sufficient coding so that access to some noncognitive structure or unconscious algorithms can be automatically attained. In prodigious savants, some genetic factors may be operative as well, since practice alone cannot account for the access to vast rules of music, art, or mathematics that seems innate in these individuals (87, 88). Once established, intense concentration, practice, compensatory drives, and reinforcement play a major role in developing and polishing the savant skills and memory made possible by this unique brain dysfunction. This suspected intermixture of neurophysiologic, genetic, and psychological factors is not new, but available technology gives us the opportunity now to better study and understand the actual component parts, especially the neurophysiologic.

New Techniques

Positron emission tomography (PET) scans, cerebral flow studies, and other brain mapping techniques now allow study of brain function, not just brain structure, and these newer modalities provide tools to study more carefully cerebral circuitry and lateralization, both of which are important in the savant. PET scans have already demonstrated that analytical strategy and the context of the stimulus are as important as the stimulus itself in determining which cerebral area or hemisphere is used in processing information (89). Such scans have been used to compare nonanalytic, musically naive subjects with analytic, musically sophisticated persons, and this work provides an interesting tool for correlation with Sloboda et al.'s study (43) of a musical savant and a professional musician with respect to tonal and atonal compositions. Methods for mapping the circuits so crucial in the unique memory capabilities and pathways of the savant are developing as well. While PET scans have not yet been carried out in the savant syndrome as such, scans of seven high-functioning adult patients who met the *DSM-III* criteria for autism in childhood did show clear differences in lateralization and various asymmetries compared to the scans of a normal control group (90). These are the kinds of research that will predominate in the future.

Such new technology for study *of* the brain, coupled with new knowledge *about* the brain, holds even more hope for learning about and learning from the savant. The savant's "memory without consciousness," which so typifies the syndrome, can be studied in almost pure culture contrast to ordinary memory—the pathway, the encoding, and the semantic, figural, and symbolic patterns. Memory formation, consolidation, and retrieval require differential involvement of the hippocampus, amygdala, and thalamus. Savant memory—so deep but so narrow, so vast but so emotionless, so limitless but so fixed—surely uses different circuitry than does ordinary memory, which is much more shallow but exceedingly wide, less vast but emotion-laden, and more limited but flexible, associative, and even creative.

No model of brain function, particularly memory, will be complete until it can include and account for the savant syndrome. This astonishing condition remains a challenge to our capabilities. The tools now available to study brain function as well as brain structure can provide a key to understanding the savant and, thus, to better understanding ourselves.

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Regular Articles

Personality Disorders in *DSM-III* and *DSM-III-R*: Convergence, Coverage, and Internal Consistency

Leslie C. Morey, Ph.D.

Although many sections of DSM-III-R *reflect few changes from* DSM-III, *the diagnostic criteria for the personality disorders involve more substantial revisions. This study examined the impact of* DSM-III-R *revisions in terms of convergence with* DSM-III, *the diagnostic coverage of patients with personality disorders, and the internal consistency of the personality disorder criteria sets. The results demonstrated a substantial divergence between* DSM-III *and* DSM-III-R *diagnoses, increased coverage accompanied by a large increase in overlap among personality disorders, and internal consistency estimates of* DSM-III-R *criterion sets comparable to those in* DSM-III.

(Am J Psychiatry 1988; 145:573-577)

The revision of *DSM-III*, known as *DSM-III-R*, has given rise to a number of significant controversies. The personality disorders are perhaps the most controversial area in which revisions have been proposed. Some discussions have centered around the suitability of new personality disorder constructs (i.e., self-defeating and sadistic personality disorder), while others have focused on the need to revise existing *DSM-III* categories to correct perceived inadequacies (1).

Although many sections of *DSM-III-R* reflect few changes from *DSM-III*, the diagnostic criteria for the personality disorders involve more substantial revisions. These changes seem to have been primarily stimulated by two factors: the personality disorder diagnoses are generally less *reliable* than other (e.g., axis I) diagnoses (2, 3), and the *coverage* of the personality disorders is seen as too narrow, which results in a large number of patients receiving "mixed" or "atypical" personality disorder diagnoses, which have little meaning (4).

It has generally been found that the coverage and the reliability of classification systems are inversely related (5, 6). That is, categorical diagnoses are typically made more reliable by decreasing the range of applicability of the category to relatively "pure" exemplars. Thus, diagnostic criteria that are applied with a high degree of precision, such as the Feighner criteria (7), leave many patients without specific diagnoses. The task force assigned to revise the personality disorders section of *DSM-III* thus had the unenviable task of attempting to increase both reliability and coverage of these disorders.

The purpose of the present study was to determine how well *DSM-III-R* criteria addressed these issues. In particular, three issues were examined.

1. To what extent do the populations identified with *DSM-III-R* personality disorder criteria correspond to those identified with *DSM-III* criteria? This question is of particular importance, since a research literature concerning the *DSM-III* personality disorders is beginning to develop. In addition, a number of methods for diagnosing personality disorders (8–11) promise to improve reliability in this area. If *DSM-III-R* criteria identify a population that is substantially different from those diagnosed with *DSM-III*, much of this research will be of limited applicability and will need to be replicated by using the new definitions.

2. What impact will the *DSM-III-R* revisions have on the coverage of the personality disorder categories? An explicit goal of *DSM-III-R* is to reduce the use of nonspecific categories such as "atypical" or "other" manifestations of various disorders. According to Peele, "*DSM-III-R* has over 100 changes in the criteria. Of the changes that will affect coverage, about 60

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expand coverage and about 20 narrow coverage. Most of the complaints that I have heard about coverage concern personality disorders. *DSM-III-R* will expand the coverage of personality disorders. This is true even if self-defeating personality disorder and sadistic personality disorder are not part of *DSM-III-R*" (4, p. 1351). Given this goal of expanded coverage, it will be important to empirically test whether or not the revisions have the intended effect. In particular, one would hypothesize that expanded coverage in the personality disorders section should result in fewer patients receiving a diagnosis of "mixed" or "atypical" personality disorder—that is, fewer patients should be identified as having a personality disorder if they do not meet the criteria for any of the 11 specific personality disorders.

3. What impact will *DSM-III-R* have on the reliability of the personality disorder categories? In addressing this issue, previous researchers (2, 12) have focused on interdiagnostician agreement to assess reliability. However, in recent years increasing attention has been given to another component of reliability—internal consistency (3, 13–15). This psychometric approach to investigating reliability has particular utility given the increasingly prominent view of the personality disorders as prototype categories (3). In the present study, the internal consistency of *DSM-III-R* definitions of personality disorder was compared to that of *DSM-III* to determine if the revisions have succeeded in improving this component of reliability.

METHOD

The sample was composed of a national sample of 291 patients who had been identified by their treating clinician as manifesting personality disorders. The case material was obtained from clinicians who were solicited at random from the *Directory of Medical Specialists* and the *Directory of the American Psychological Association*. A total of 101 completed questionnaires were received from psychiatrists and 190 from psychologists. All clinicians were at the M.D. or Ph.D. (clinical psychologist) level. Clinicians were asked to provide information concerning two (maximum) of their patients; information for the study was provided by 170 different clinicians. Stipulations for participating in the study included the following: 1) all patients must have been diagnosed as having a personality disorder, and 2) the clinicians must have had a minimum of 10 hours of contact with the patient during the past year. Given these restrictions, it was anticipated that an extensive mailing of invitations would be needed to obtain a reasonable sample size; of the clinicians who acknowledged receipt (by means of a prepaid postcard) of the initial invitation (a letter outlining eligibility requirements), there was a 36% response rate. Of the clinicians who indicated an interest in participating in the study, there was a 76% response rate. All clinicians received an honorarium of $20 following their participation.

TABLE 1. Diagnostic Convergence Between *DSM-III* and *DSM-III-R* for 291 Patients With Personality Disorder

Personality Disorder	Percent of Patients With Diagnosis: *DSM-III*	Percent of Patients With Diagnosis: *DSM-III-R*	Kappa	Z
Borderline	32.0	33.3	0.969[a]	62.43
Narcissistic	6.2	22.0	0.378[a]	4.56
Histrionic	21.6	21.6	0.656[a]	11.83
Antisocial	5.8	6.2	0.726[a]	8.06
Avoidant	11.3	27.1	0.447[a]	6.43
Dependent	14.1	22.3	0.543[a]	8.10
Compulsive	8.9	7.9	0.531[a]	5.39
Passive-aggressive	8.2	12.4	0.407[a]	4.12
Paranoid	7.2	22.0	0.327[a]	3.82
Schizoid	1.4	11.0	0.091	0.60
Schizotypal	17.2	9.3	0.602[a]	8.24
Atypical, mixed	29.2	22.3	0.581[a]	10.11

[a] $p<0.001$.

Although it is possible that the 10-hour restriction may have yielded an unrepresentative sample of patients with personality disorder, the prevalence rates of the different personality disorders obtained in this sample were very similar to rates reported in other studies that examined all 11 specific *DSM-III* personality disorders. For example, Pfohl et al. (14), using a structured interview, assigned diagnoses by determining the presence or absence of each *DSM-III* personality disorder criterion. The correlation between the present study's base rates of the 11 specific and one nonspecific *DSM-III* diagnoses (presented in table 1) and those reported by Pfohl et al. was 0.90. Thus, at least with respect to the distribution of diagnoses, the present sample appears to be representative.

Data from both psychiatrists and psychologists were collected by using the Vanderbilt Personality Disorders Diagnostic Survey (available from the author). This questionnaire included a checklist of 166 features describing the 11 specific axis II personality disorders. These features consisted of all specific diagnostic criteria for personality disorders included in *DSM-III* and in *DSM-III-R* (July 1, 1985, draft). The diagnostic criteria were arranged in random order to minimize possible halo effects between symptoms (3).

From the checklist information provided by the clinicians, *DSM-III* and *DSM-III-R* diagnoses were calculated algorithmically by using a computer program designed to precisely follow the decision rules presented in these two classifications. In other words, if a clinician indicated that a patient manifested at least five of the eight specific *DSM-III* criteria for borderline personality disorder, the patient was assigned to that diagnostic group (the criterion for passive-aggressive personality that excludes individuals with other personality disorders was ignored in all analyses). Similarly, if a patient was identified as meeting at least five of the nine specific *DSM-III-R* criteria for passive-aggressive personality disorder, the patient was assigned to that diagnostic group. All *DSM-III-R* assignments were made by using the final *DSM-III-R* criteria, which for most diagnoses were similar or virtually identical to those in the July 1, 1985, draft criteria. However, two diagnoses—histrionic and antisocial—contained criteria that could not be easily assessed. For *DSM-III-R* histrionic personality disorder, one preliminary *DSM-III-R* criterion (style of speech characterized by exaggeration and hyperbole) had to be substituted for a somewhat related, final *DSM-III-R* criterion (style of speech that is excessively impressionistic and lacking in detail) which was not in the draft version. For *DSM-III-R* antisocial personality disorder, certain aspects of the historical criterion B contained in the final version of *DSM-III-R* were not assessed (i.e., onset before age 15: using weapons in fights, forcing someone into sexual activity, physically cruel to animals or people). Given that these last three criteria reflect more seriously deviant and hence statistically less frequent behavior than other features of this criterion (e.g., lying, fighting, stealing, truancy), it might be expected that individuals displaying the more serious behaviors would also be expected to display at least three of the less serious features. As such, the exclusion of these features should not substantially alter the population of individuals who meet this criterion. The final version of the *DSM-III-R* criteria for antisocial personality disorder that reflected behavior during adulthood (criterion C) was represented verbatim in the study material.

RESULTS

The patient sample included more women (56%) than men, a finding noted in other studies with comparable samples (16). Most of the patients were white (92% were white; most of the others were black), and the average age was 35 years. The patients were distributed roughly equally across socioeconomic groups. The patients were typically seen on an outpatient (85%) basis. The most common specific *DSM-III* axis I diagnosis was dysthymic disorder (21.3%); no other major axis I disorder was diagnosed in more than 15% of the sample.

Agreement Across Diagnostic Systems

Table 1 presents the agreement between *DSM-III* and *DSM-III-R* axis II for 291 patients with personality disorder. The table includes the percent of the total sample receiving each diagnosis under the two systems and the agreement (in terms of the kappa coefficient) between the two diagnostic schemes (the kappa coefficient represents an agreement index corrected for chance correspondence). The significance levels of the kappa coefficients, assessed with the Z-test described by Bartko and Carpenter (17), are also presented in this table. From these results, it is apparent that there was a great deal of variation in the agreement between the two systems. For some diagnoses, there was near total convergence; for example, the kappa between borderline diagnoses under *DSM-III* and *DSM-III-R* was 0.969. However, for most other diagnoses, the convergence was much lower. Most notable in this regard was schizoid personality disorder, for which the between-systems kappa (0.091) did not even reach statistical significance. This last finding demonstrates that the schizoid criteria in *DSM-III* identify a population of patients which is markedly different from that diagnosable under *DSM-III-R*.

It is interesting to note that the large increase in schizoid diagnoses with *DSM-III-R* was accompanied by a substantial decrease in schizotypal diagnoses. A detailed examination of these diagnoses reveals that many of the patients with a *DSM-III-R* diagnosis of schizoid personality disorder would have been diagnosed as schizotypal with *DSM-III*. Specifically, of the patients with a *DSM-III-R* diagnosis of schizoid personality disorder, 50% met *DSM-III* criteria for schizotypal personality disorder, but only 6% received a *DSM-III* diagnosis of schizoid personality disorder.

Impact on Diagnostic Coverage

As discussed earlier, an explicit goal of *DSM-III-R* was to reduce the use of categories such as "atypical" or "other" personality disorder by expanding the coverage of the categories of specific personality disorders. As can be seen in table 1, it was generally true that *DSM-III-R* criteria had broader coverage than those in *DSM-III*, since 1) the rate of atypical, mixed declined to 22.3% from 29.2%, and 2) only two specific personality disorders (schizotypal and compulsive) decreased in observed frequency. These findings indicate that the *DSM-III-R* personality disorder criteria are somewhat less restrictive than their *DSM-III* counterparts. In some cases, the difference is marked: for example, with *DSM-III-R* there was an 800% increase in the rate of schizoid personality disorder and a 350% increase in narcissistic personality disorder.

Given the sharp increases in frequency of diagnosis of many of the personality disorders and the relatively modest decrease in diagnoses of atypical, mixed personality disorder, it is possible that this decrease may have been gained at the expense of a substantial increase in the diagnostic overlap among personality disorders. The relevant data were as follows: with *DSM-III*, 29.2% of the sample did not qualify for any specific personality diagnosis, 34.4% met the criteria for one disorder, and 36.4% met the criteria for at least two specific personality disorders; with *DSM-III-R*, the comparable figures were 22.3%, 25.8%, and 51.9%. It is worth noting that the former figures actually overestimate the overlap among *DSM-III* disorders, since the *DSM-III* criterion which prohibits overlap between any other personality disorder and passive-aggressive personality disorder was ignored. These results make it apparent that the modest increase in personality disorder coverage with *DSM-III-R* was indeed obtained at the expense of a more substantial increase in diagnostic overlap.

TABLE 2. Personality Disorder Diagnostic Overlap of *DSM-III-R* Criteria for 291 Patients With Personality Disorder

Criterion	Percent of Criterion Group Also Receiving Indicated *DSM-III-R* Diagnosis										
DSM-III-R Diagnosis	Borderline	Narcissistic	Histrionic	Antisocial	Dependent	Avoidant	Obsessive-Compulsive	Passive-Aggressive	Paranoid	Schizoid	Schizotypal
Borderline		30.9	36.1	8.2	34.0	36.1	2.1	13.4	32.0	6.2	9.3
Narcissistic	46.9		53.1	15.6	26.6	35.9	10.9	28.1	35.9	14.1	14.1
Histrionic	55.6	54.0		9.5	30.2	31.7	4.8	19.0	28.6	4.8	7.9
Antisocial	44.4	55.6	33.3		11.1	16.7	0.0	50.0	27.8	5.6	5.6
Dependent	50.8	26.2	29.2	3.1		49.2	9.2	16.9	29.2	9.2	12.3
Avoidant	44.3	29.1	25.3	3.8	40.5		16.5	15.2	39.2	21.5	20.3
Obsessive-compulsive	8.7	30.4	13.0	0.0	26.1	56.5		26.1	21.7	21.7	13.0
Passive-aggressive	36.1	50.0	33.3	25.0	30.6	33.3	16.7		30.6	16.7	11.1
Paranoid	48.4	35.9	28.1	7.8	29.7	48.4	7.8	17.2		23.4	25.0
Schizoid	18.8	28.1	9.4	3.1	18.8	53.1	15.6	18.8	46.9		37.5
Schizotypal	33.3	33.3	18.5	3.7	29.6	59.3	11.1	14.8	59.3	44.4	

TABLE 3. Internal Consistency of Personality Disorder Criteria of *DSM-III* and *DSM-III-R* for 291 Patients With Personality Disorder

Personality	Median Intercriterion Correlation	
Disorder	*DSM-III*	*DSM-III-R*
Borderline	0.258	0.239
Narcissistic	0.210	0.174
Histrionic	0.187	0.244
Antisocial	0.234	0.225
Avoidant	0.192	0.198
Dependent	0.343	0.195
Compulsive	0.099	0.100
Passive-aggressive	0.227	0.223
Paranoid	0.139	0.293
Schizoid	0.108	0.154
Schizotypal	0.197	0.197

The specific nature of diagnostic overlap in the *DSM-III-R* system is described in table 2 (similar values were obtained for *DSM-III* and are available from the author). A comparison of these values to comparable figures from *DSM-III* affirms the greater overlap among personality disorders with the revised criteria. For example, under *DSM-III* only four personality disorders (narcissistic, histrionic, paranoid, and schizoid) had an overlap of at least 50% with another personality disorder. When *DSM-III-R* criteria were used, eight of the 11 specific disorders manifested this degree of overlap. This overlap reflects a serious problem for researchers who are interested in identifying relatively pure criterion groups.

Impact on Internal Consistency

Internal consistency estimates for the criteria that define the 11 specific personality disorders, for both *DSM-III* and *DSM-III-R*, are presented in table 3. The values represent the median intercriterion correlation within each of the personality disorders; thus, the typical intercorrelation among the eight *DSM-III* criteria for borderline personality was 0.258. Although other research has used coefficient alpha as a measure of *DSM-III* internal consistency (4, 14), the median interitem correlation has the advantage of being less affected by the different lengths of the criterion lists for the different personality disorders. As in any examination of internal consistency, it should be noted that halo effects between symptoms may artificially inflate intercriterion correlations; the random presentation of criterion features was used in an attempt to minimize the impact of this phenomenon.

Table 3 reveals that, considered globally, the internal consistency of *DSM-III-R* criteria was comparable to that of *DSM-III*. Although the internal consistency of some criterion sets (e.g., dependent personality disorder) declined substantially, other disorders (e.g., paranoid personality disorder) demonstrated a marked improvement with *DSM-III-R*. Thus, the expanded coverage of most disorders evidenced in table 1 was not achieved at the expense of internal consistency. However, there was a trend for disorders with substantial increases in coverage, such as narcissistic and dependent personalities, to show decreased internal consistency.

DISCUSSION

In this examination of the *DSM-III-R* revisions in criteria for personality disorder, the results demonstrated that the revisions will have a considerable impact on the nature of the populations identified with these criteria. Although some specific personality disorders, such as borderline, will be relatively unchanged with the new diagnostic standards, others will be drastically affected. For example, with the new criteria one could predict an eightfold increase in schizoid personality disorder and a threefold increase in narcissistic personality disorder. The generally limited agreement between personality disorder diagnoses made with *DSM-III* and *DSM-III-R* suggests that researchers and clinicians should exercise caution in interpreting these two manuals as directly comparable, despite the identical names that are used.

The substantial nature of these revisions is not necessarily unwarranted; the definitions of specific personality disorders have been criticized for poor reliability and inadequate coverage. The results of the present study indicate that the *DSM-III-R* revisions will increase the coverage of these disorders without lowering their reliability (as defined by internal consistency). This accomplishment must be considered in light of the fact that coverage and interrater reliability are generally found to be inversely related. It might also be anticipated that coverage and internal consistency would be inversely related. For example, broadly defined personality constructs will require a variety of different behaviors as diagnostic criteria. These broad constructs will be applicable to a greater range of patients, but the set of behaviors that define the syndrome will be more disparate (and hence less internally consistent) than those which define a fairly narrow construct. Thus, a broader construct such as borderline personality disorder may be applicable to more patients than a fairly narrow construct such as transient tic disorder, but it is likely that behaviors pertinent to the latter diagnosis will be more internally consistent than those which pertain to the former. Thus, the finding that *DSM-III-R* has increased the coverage of personality disorders without lowering their internal consistency is impressive.

The primary difficulty with *DSM-III-R* criteria is that the revisions substantially increase the amount of diagnostic overlap between the different personality disorders. Traditionally, classification systems in psychiatry have been consistent with those in other branches of medicine in using categorical constructs. Under such systems, differential diagnosis is encouraged in an attempt to keep diagnostic overlap to a minimum; most diagnostic systems have (implicitly or explicitly) used diagnostic hierarchies to maintain the tradition of unitary diagnosis (18). Among other problems, the substantial overlap among the personality disorders in *DSM-III-R* will make it difficult to establish reasonably pure criterion groups for research purposes. If categorical (as opposed to dimensional) systems of personality diagnosis are deemed advantageous, future diagnostic systems could use a hierarchical scheme (19) based on empirical relationships among the personality disorders such as those presented here. A hierarchical strategy, implemented through the use of exclusion criteria, would reduce diagnostic overlap and thereby enhance the utility of a categorical approach to personality disorder diagnosis.

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Deficit and Nondeficit Forms of Schizophrenia: The Concept

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The authors provide a rationale for distinguishing the primary, enduring negative symptoms of schizophrenia (termed "deficit symptoms") from the more transient negative symptoms secondary to other factors. They argue that the former are more likely to provide a basis for meaningful subtyping of the schizophrenic syndrome, while the latter are more likely to respond to currently available treatments. They describe their experience in using clinical judgment based on longitudinal observations to identify deficit and nondeficit subtypes of schizophrenic patients and propose criteria for defining schizophrenia with the deficit syndrome.

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Two quite different psychopathologic processes are associated with the concept of schizophrenia. Strauss et al. (1) discussed these dimensions in accordance with the concept of positive and negative symptoms. Berrios (2) credits Reynolds's 1858 contribution with introducing the positive and negative symptom terminology into the neurology literature and believes that de Clerambault first stressed the distinction in the psychiatric literature. Most modern discussions of the positive-negative dichotomy emphasize the contributions of Hughlings Jackson (3). In neurology the term "negative symptoms" refers to direct loss of normal function resulting from a pathologic process, while the term "positive symptoms" refers to active processes expressed in an excessive or distorted way because of the loss of normal inhibitory mechanisms. With respect to schizophrenia, positive symptoms include hallucinations, delusions, certain forms of thought disorder, and some bizarre behaviors. Negative symptoms include restricted affect, diminished social drive, ideational constriction, and diminished emotional range. This use of the terms "positive symptoms" and "negative symptoms," however, differs from Jackson's in two respects. First, the relationship between the type of symptom and the nature of the tissue destruction or damage cannot be presently defined. Second, a criterion of temporal stability distinguishes positive from negative symptoms. Specifically, the assumption is made that negative symptoms, when present, are enduring features of the schizophrenic illness, whereas positive symptoms may fluctuate dramatically over time. This parallels Snezhnevsky's (4) distinction between flexible and inflexible symptoms and is reflected in the description by Wing and Brown (5) of a poverty syndrome in contrast to the florid psychotic symptoms. In 1974 Strauss et al. (1) also noted a third category of symptoms manifested in social behaviors and not readily classified positive or negative, and Carpenter (6) recently suggested a fourth category for defining the neurological manifestations of schizophrenia. Carpenter and Buchanan (7) now delineate five domains of psychopathology that merit independent investigation (e.g., genetic linkage studies of putative phenotypes) and may be used to subgroup cohorts of schizophrenic patients. These domains are hallucinations and delusions, cognitive impairment, dissociative affective processes, deficit processes, and neurological processes.

THE CONCEPT OF POSITIVE AND NEGATIVE SYMPTOMS

We believe the germinal influence in conceptualizing separable pathologic processes was that of Kraepelin (8), with his clear definition of the two disorders of dementia praecox: weakening of the will and deterioration of the personality contrasted with dissociation among thought, feeling, and behavior.

Crow and colleagues (9–12) used the distinction between positive and negative symptoms to postulate two types of schizophrenia. Type I is characterized by acute onset, usually normal intellectual function, normal brain structure, good response to antipsychotic drugs, possibly increased D_2 dopamine receptors, and the absence of negative symptoms. In contrast, type II schizophrenia is characterized by insidious onset, intellectual deterioration, enlarged cerebral ventricles, poor response to antipsychotic drugs, and prominent negative symptoms. While all schizophrenic patients would be expected to exhibit positive symptoms at times during the course of their illness, the presence or

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absence of negative symptoms is the key distinguishing clinical attribute. Furthermore, Crow and colleagues maintain that patients who lack negative symptoms early in their illness may later develop them; once severe negative symptoms develop they persevere, and the type II designation is considered irreversible. It is important to note that the distinction between type I and type II is based on a series of attributes, only one of which is the presence or absence of negative symptoms. Thus, the typology of type I and type II schizophrenia is not synonymous with "positive" and "negative" schizophrenia.

The usefulness of the positive-negative distinction has been studied in the past few years. Andreasen and Olsen (13) used a detailed clinical assessment of affect and thought disturbance to construct three cross-sectional subtypes of schizophrenia that occurred with about equal frequency in their inpatient unit. Positive schizophrenia was characterized by the prominence of hallucinations, delusions, or marked positive thought disorder, with minimal negative symptoms or none at all. Negative schizophrenia, conversely, was defined by the prominence of symptoms such as poverty of speech, poverty of content of speech, restricted affect, psychomotor retardation, and anhedonia, with minimal positive symptoms or none. Patients who failed to meet criteria for both sets of features or had a substantial number of both were classified as "mixed." In support of the validity of the positive-negative distinction, Andreasen and Olsen (14) found that the patients with negative symptoms had less education, poorer premorbid adjustment, a lower employment rate, higher ventricle-brain ratios on CAT scans, poorer performance on the Mini-Mental State examination, greater frequency of left-handedness, and higher global ratings of impairment at both admission and discharge. A moderate but significant negative correlation was obtained between positive and negative symptoms for the group as a whole, supporting the view that the positive-negative distinction represented opposing ends of a symptom continuum. Andreasen (15) has also discussed the different implications of conceptualizing negative symptoms at the levels of disease, syndrome, and symptom.

Pogue-Geile and Harrow (16) evaluated positive and negative symptoms in a follow-up study composed primarily of a relatively stable outpatient population of schizophrenic and depressed patients. The infrequency of severe negative symptoms in the depressed group suggests that the negative symptom complex is not just a special kind of affective disorder (i.e., one in which dysphoric mood diminishes intrapsychic functions). Schizophrenic patients who had poor premorbid features were more likely to have negative symptoms and impaired functioning at the time of assessment. No correlation between positive and negative symptoms was observed, which thus supports the Strauss et al. (1) hypothesis of independent dimensions rather than the bipolar continuum approach of Andreasen and Olsen (13).

In another study involving chronic schizophrenic patients, Pogue-Geile et al. (unpublished 1983 paper) found that while negative symptoms were significantly associated with intellectual deficits, positive symptoms were not, and they again found that negative and positive symptoms were uncorrelated. This independence of negative and positive symptoms was also supported by the work of Crow (9, 11) and by the results of a detailed analysis of the interrelationship of these symptoms by Lewine et al. (17).

Refining the Terminology

With the growing interest in this area of subtyping, there is a need for careful delineation of terminology (18) that explicitly considers two important distinctions. First, negative symptoms must be distinguished from disorders in relating (1). Social withdrawal is not a direct measure of negative symptoms. Rather, it can be the complex outcome of a range of schizophrenic symptoms, either positive or negative or mixed, interacting with the specific interpersonal and cultural environment in which the patient is embedded. Loss of social drive is considered a negative symptom, whereas paranoid social withdrawal is not. Thus, inadequacies in relating are not, ipso facto, negative symptoms.

Second, the behaviors and inner experiences that are postulated to be negative symptoms may themselves be either primary or derivative. The clinician, when encountering putative negative symptoms such as apathy, avolition, anhedonia, and anergia, should attempt to discern whether factors such as drug effects, dysphoric mood, self-protective reduction of stimulation in the face of psychotic decompensation, and absence of social stimulation are causative. It is important to differentiate derivative or secondary negative symptoms from those that are primary or direct expressions of a pathologic dimension of schizophrenia. The treatment and course of secondary negative symptoms are expected to be responsive to temporal changes in the factors with which they are associated (19). For example, depression-induced anhedonia should improve with resolution of the depression. Primary negative symptoms are expected to be less responsive (although not necessarily unresponsive) to state changes, and their cause is as enigmatic as the etiology of schizophrenia; specific treatment is not presently available, and full remission is not expected once primary negative symptoms have become enduring traits (19). The concept of primary symptoms does not exclude negative symptoms as transitory, but differentiation of primary from secondary symptoms is vexing when symptom manifestation is brief (19).

Differential diagnosis and etiologic inference regarding negative symptom manifestations are commonplace challenges for the clinician. They are of vital importance, since specific treatment is directly dependent on the clinician's judgment. The same challenges are faced by the investigator who applies the criteria for the deficit-nondeficit distinction that we have listed in appendix 1. We have detailed a treatment-oriented approach to this task elsewhere (19).

Deficit Symptoms

"Negative symptoms" has gained a place in clinical jargon and is now widely used as a descriptive term. Confusion has emerged, however, because the critical distinctions between negative symptoms and disorders in relating and between primary and secondary attributes have not been established. We propose using "negative symptoms" as a descriptive term without implications concerning cause, stability, or duration. The term "deficit symptoms" may then be used to refer specifically to those negative symptoms that are present as enduring traits and that are not considered secondary. Deficit symptoms are present during and between episodes of positive symptom exacerbation. They can be observed regardless of the patient's medication status and are not specifically responsive to anticholinergic drugs or antipsychotic drug withdrawal. Some aspects of poor premorbid or early morbid adjustment may be manifestations of the deficit syndrome preceding the initial psychotic episode. In this definitional framework, patients with the nondeficit type of schizophrenia may have negative symptoms, but these would be expected to demonstrate a greater fluctuation, a lack of persistence, and a temporal association with possible underlying causes (e.g., dysphoric states, drug status). The patient with deficit symptoms may also have changes in symptom intensity and superimposed secondary negative symptoms, but a primary and enduring core of negative symptoms must be present. This approach to deficit symptoms requires clinical judgment based on longitudinal observation rather than a cross-sectional assessment to establish the presence or absence of the symptoms. For purposes of distinguishing interesting subtypes of schizophrenia (e.g., type II schizophrenia), we believe that deficit symptoms, rather than negative symptoms, are critical.

The distinction may also clarify the diagnostic relevance of negative symptoms. It is evident that secondary negative symptoms, as we have just defined them, will not serve to discriminate diagnostic class. However, as enduring manifestations, deficit symptoms such as anhedonia and blunted affect have long been considered to be core manifestations of schizophrenia (8) and basic discriminating features common to various approaches to differential diagnosis (20).

THE PRESENT STUDY

We have provided a conceptual basis for the distinction of deficit and nondeficit schizophrenia and have argued that it is likely to be valuable in reducing the heterogeneity of the schizophrenic syndrome. We expect the distinction between deficit symptoms and negative symptoms to clarify the study of each. In the exploratory study that we describe here, we addressed the following questions. 1) Can schizophrenic outpatients be confidently categorized by clinicians as having deficit or nondeficit schizophrenia? 2) Do patients so categorized actually differ, as intended by the definitions, with respect to the endurance of negative symptoms? 3) Do these patients differ on variables reflecting demographic factors, course of illness, and level of current positive and negative symptoms?

Identification of Patients With Deficit and Nondeficit Schizophrenia

Method. The subjects were participants in an outpatient research clinic. They had an overall clinical diagnosis of schizophrenia according to *DSM-III* criteria and met the Research Diagnostic Criteria (21) for schizophrenia or schizoaffective disorder, mainly schizophrenic. The mean duration of the subjects' participation in the clinic was 29 months (range=2–74 months), providing the opportunity for longitudinal observation.

The concept of the deficit syndrome was presented to the clinical staff. A written statement defining the relevant features (available from the authors on request) was provided, and this was followed by a detailed discussion. The distinction between deficit and negative symptoms was emphasized. Key symptoms, at least two of which should be present in an enduring manner for any case labeled as the deficit subtype, were delineated: flattened or restricted affect, anhedonia, poverty of speech with curbing of the ideational field, lack of a sense of purpose, and diminished social drive. The members of the clinical staff were then asked to assign patients to deficit or nondeficit subgroups. When several clinicians were familiar with a given patient, discussion among them led to a consensus assignment. All patients were assigned to one of three groups: definitely deficit, definitely nondeficit, and uncertain. For patients in the uncertain category, clinicians were asked whether their inability to assign a patient to the deficit or nondeficit group was due to inadequate information or clinical ambiguity. Judgments were based on all available information, including treatment records, history obtained from patients and relatives, and direct observation of patients. As a result of this process, explicit and operationalized criteria were articulated (see appendix 1). As a final check, the cases of patients assigned to the deficit and nondeficit groups were reviewed by one of us (D.W.H.) to ensure that the former met and the latter did not meet our formalized criteria for schizophrenia with deficit syndrome.

Results. Of the 103 patients considered, 15 were confidently assigned to the deficit group, 64 to the nondeficit group, and 24 to the uncertain group. For this last group, the inability to categorize was based on inadequate information in 10 cases, ambiguity of the clinical presentation in three cases, and some mixture of inadequate information and ambiguity in 11 cases.

The deficit group patients had a mean±SD of 4.6±0.6 of the five key symptoms judged to be present by at least one of the informed clinicians. The mean for the nondeficit group patients was 0.8±1.5.

Discussion. This diagnostic exercise indicated that the majority of schizophrenic outpatients could be confidently characterized as having the deficit or nondeficit subtype by the clinicians involved in their care, demonstrating the feasibility of applying the deficit syndrome concept to individual patients. Discussion of all information and use of consensus judgments ensured agreement in these cases, but this process does not assess reliability. However, as a first approximation to assessing reliability, a senior clinician familiar with most of the patients in the clinic was asked to independently assign the first 44 cases. He had been absent from the clinic during the discussions and assignments of these cases. His independent classifications agreed in 42 of the 44 instances. He spontaneously noted that he was not sufficiently familiar with the situation to judge one of the two discordant cases. Formal reliability testing based on explicit criteria derived from this work is necessary, but this experience suggests that the deficit-nondeficit distinction can be reliably made by clinicians.

Endurance and Stability of Negative Symptoms Over Time

Method. The criteria for the deficit syndrome used by the rating clinicians included the continued presence of negative symptoms over time, in contrast to the secondary and episodic negative symptoms that may occur in patients with nondeficit schizophrenia. To evaluate the success of this diagnostic procedure in capturing this distinction in negative symptom stability over time, data from repeated administrations of the Brief Psychiatric Rating Scale (BPRS) (22) were examined. Item 16 is blunted affect, a putative negative symptom, and factor 2 (anergia-withdrawal) is an imperfect approximation of a composite of negative symptoms. Four consecutive ratings, each about 4 weeks apart (mean±SD=3.6±1.5 weeks) and obtained within a 6-month period, were available for 13 patients from the deficit group. These ratings were compared with those of 13 patients from the nondeficit group who were of similar age, education, sex, and race. We used equal numbers of both groups of patients in order to prevent bias toward significance, which can occur with grossly different sample sizes, and to minimize the influence of age, education, sex, and race. These ratings were made on a routine basis as a function of the subjects' participation in the clinic; they were completed independently before this study of the deficit syndrome. Each rating epoch was cross-sectional, representing symptom status during the preceding week and observation at the time of rating.

Results. For the deficit group patients, symptoms were rated as present (score of 2 or more on a 7-point scale) on 46 of the 52 occasions for the blunted affect item and on 51 of the 52 occasions for the anergia-withdrawal factor. In contrast, the nondeficit group patients displayed symptoms on 15 and 30 of the 52 occasions for blunted affect and anergia-withdrawal, respectively. The difference in long-term stability of negative symptoms between groups was also reflected in the intraclass correlation (ICC) for both anergia-withdrawal and blunted affect computed over the four occasions for each subject. Scores for anergia-withdrawal were significantly more correlated (χ^2=4.16, df=1, $p<0.05$) for the deficit group patients (ICC=0.62, df=12, 39, $p<0.005$) than for the patients in the nondeficit group (ICC=0.18, df=12, 39, n.s.) Scores for blunted affect were more correlated, but not significantly so (χ^2=0.66, df=1, n.s.), for the deficit group patients (ICC=0.55, df=12, 39, $p<0.025$) than for the nondeficit group patients (ICC=0.37, df=12, 39, n.s.).

Discussion. The BPRS afforded only a limited assessment of negative symptoms, but it is evident that negative symptoms were almost always present in deficit group patients and only episodically so in patients in the nondeficit group. Also, the intensity of negative symptoms was more consistent in the deficit group patients over time. Since the presence of enduring negative symptoms is part of our definition of the deficit syndrome, these findings require validation by other measures. However, the findings do demonstrate that the procedure for assigning patients to deficit and nondeficit groups on the basis of the comprehensive judgment of informed clinicians does succeed in capturing this distinction in the endurance and stability of negative symptoms.

The Deficit Syndrome and Demographic and Clinical Variables

Method. The deficit and nondeficit groups were compared on the following variables, which were routinely assessed at entry into the clinic: age, education, handedness, sex, race, age at first hospitalization, number of previous hospitalizations, total Strauss-Carpenter prognostic scale (23) score, and scores on the BPRS psychosis-thinking disorder, anergia-withdrawal, depression, and excitement-disorientation factors.

Results. The patients in the deficit group were more symptomatic on the anergia-withdrawal factor and had poorer prognostic scale scores (see table 1). They were also more likely to be male (13 of 15 patients in the deficit group were male, and 32 of 64 in the nondeficit group were male; χ^2=6.14, df=1, $p<0.05$). Patients in the deficit and nondeficit groups did not differ in positive psychotic symptoms, age at first hospitalization, number of previous hospitalizations, age, education, race, or handedness.

Discussion. Since the anergia-withdrawal factor is the BPRS factor that most relates to negative symptoms, it is not surprising that the deficit group had a higher score on this dimension. The similarity of the

TABLE 1. Clinical and Demographic Features of Patients With Deficit (N=15) and Nondeficit (N=64) Schizophrenia

Variable	Deficit Group Mean	Deficit Group SD	Nondeficit Group Mean	Nondeficit Group SD	F (df=1, 77)
BPRS score	1.8	0.4	1.7	0.5	0.66
Factor 1 (psychosis-thinking disorder)	1.7	0.7	1.7	0.8	0.01
Factor 2 (anergia-withdrawal)	2.5	1.1	1.7	0.6	10.42[a]
Factor 3 (depression)	1.7	0.6	1.9	0.7	0.55
Factor 4 (excitement-disorientation)	1.2	0.2	1.2	0.4	0.04
Strauss-Carpenter prognostic scale score	3.2	2.7	5.4	2.7	7.64[a]
Age at first hospitalization (years)	24.6	6.2	23.6	6.8	0.25
Number of hospitalizations	3.5	3.9	4.5	4.1	0.68
Current age (years)	27.9	6.2	29.0	6.9	0.32
Education (years)	11.9	2.1	12.6	1.8	1.89

[a] $p<0.05$.

deficit and nondeficit groups on the psychosis-thinking disorder factor suggests that positive symptoms are an independent dimension. This is compatible with the views of Strauss et al. (1), Crow (9, 11), and Pogue-Geile and Harrow (16 and unpublished 1983 paper). It is not compatible with the position of Andreasen et al. (13, 14), who see positive and negative symptoms as opposite poles of a continuum. The similarity on measures of hospitalization may reflect the fact that positive rather than negative symptoms are the main determinants of hospitalization. The poorer prognostic scores of the patients in the deficit group suggest poor premorbid and early morbid functioning, with impairment in several functional domains, which is consistent with the longitudinal view that we espouse.

The greater frequency of males in the deficit group is interesting. Lewine (24) has reviewed the evidence for sex-related differences in schizophrenic illness. It may be that the deficit syndrome marks a form of the schizophrenic illness for which males have a particular propensity. If a preponderance of males with the deficit syndrome is found in larger, representative samples, it could be suggested that schizophrenia with the deficit syndrome is among a group of neurologically based behavioral disorders such as autism, dyslexia, and attention deficit disorder that are characterized by early onset and male predominance. Geschwind and Galaburda (25) have hypothesized that this group of illnesses is related to a testosterone-dependent delay in left hemispheric maturation that makes the left hemisphere more vulnerable to impairment and injury in males. This hypothesis is compatible with evidence suggesting left hemisphere underactivation in poor-prognosis withdrawn schizophrenia (26 and unpublished 1984 paper by J. Gruzelier et al.). Such a notion would also fit with observations by Crow and colleagues (9–12) that type II schizophrenia is characterized by evidence of neurological disease, such as increased neurological abnormalities and enlarged ventricles. The CAT scan data of Andreasen et al. (14) also support this view. Our data from this small sample, however, did not reveal any trend toward greater frequency of left-handedness in the deficit group.

CONCLUSIONS

It is generally accepted that schizophrenia is a heterogeneous clinical syndrome, and a number of current investigators are using negative symptoms in an attempt to define a putative disease entity. We believe that this effort is already confounded and potentially undermined by failure to clearly distinguish negative symptoms that constitute longstanding psychopathologic traits from those that are more effervescent—and often secondary—state phenomena. For the purpose of defining a more homogeneous subtype of schizophrenia, the former are of interest. For some other purposes (e.g., study of acute treatment effects), the latter may be the focus. In either case, investigative work and clinical inference are compromised if the distinction is not established.

In this report we have described the concept and proposed diagnostic criteria for the distinction between deficit symptoms and negative symptoms (appendix 1). Our experience suggests that well-informed clinicians can categorize the majority of schizophrenic outpatients into those with and those without the deficit syndrome. There are encouraging preliminary indications that this can be done reliably. In the present study, the characteristics of patients so categorized reflected the definitional distinctions in level, in endurance, and in stability of negative symptoms.

To validate the deficit-nondeficit distinction, it is necessary to demonstrate that it distinguishes patients in terms of variables other than those intrinsic to the classification process. In this regard, the finding of poorer prognostic scores and a higher proportion of males in the deficit group is relevant. A promising area for further efforts at validation is the examination of neuropsychological differences between deficit and nondeficit groups. Findings to date would lead to the expectation of greater impairment in the deficit group. Neuropsychological test data confirming the deficit-nondeficit distinction in this cohort are reported elsewhere (27). Together with the literature we have cited, these data reinforce our view that the deficit form of schizophrenia (or overlapping constructs of type II or negative symptom schizophrenia) is associated with a more severe pathophysiologic process.

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APPENDIX 1. Criteria for Schizophrenia With Deficit Syndrome

In order to operationalize the designation of the deficit syndrome in accordance with the conceptual definition developed in this paper, we offer the following criteria for schizophrenia with deficit syndrome.

1. The patient meets *DSM-III* criteria for schizophrenia.
2. At least two of the following negative symptoms are present:
   a. Restricted affect
   b. Diminished emotional range
   c. Poverty of speech with curbing of interest and decrease in curiosity
   d. Diminshed sense of purpose
   e. Diminished social drive
3. The negative symptoms are not fully accounted for by one or more of the following:
   a. Depression or anxiety
   b. Drug effect
   c. Environmental deprivation
4. Some combination of two or more of the negative symptoms listed above has been present for the preceding 12 months, and these symptoms were always present during periods of clinical stability (including chronic psychotic states) or during recovery from psychotic exacerbation. These symptoms may not be detectable during transient episodes of acute psychotic disorganization or decompensation.

Patients meeting only criterion 1 can be designated as schizophrenic without negative symptoms. Patients meeting criteria 1 and 2 and possibly 4, but not meeting criterion 3, can be designated as schizophrenic with secondary negative symptoms. Patients meeting all four criteria can be designated as schizophrenic with deficit syndrome. Patients meeting criteria 1, 2, and 3, but not criterion 4, could either be schizophrenic with primary, nonenduring negative symptoms or with time will meet the full criteria for schizophrenia with deficit syndrome. Clearly, the former designation can be made with confidence only after negative symptoms have remitted. However, since there may be considerable research interest in this group, it is desirable to have criteria that exclude most cases that will progress to schizophrenia with deficit syndrome without waiting to see whether current negative symptoms remit. Hence, we propose the following criteria for schizophrenia with primary, nonenduring negative symptoms.

1. The patient meets criteria 1, 2, and 3 for schizophrenia with deficit syndrome.
2. The patient does not meet criterion 4 for schizophrenia with deficit syndrome.
3. The patient has had two or more prior periods of primary negative symptom (criteria 1, 2, and 3 for schizophrenia with deficit syndrome) followed by at least 3 months of remission of negative symptoms.
4. The current period of primary negative symptoms is of not more than 4 months' duration.

This would leave a residual, ambiguous category of patients meeting criteria 1, 2, and 3 for schizophrenia with deficit syndrome but not meeting full criteria for schizophrenia with primary, nonenduring negative symptoms. Such patients would require further observation to determine whether they subsequently meet criteria for schizophrenia with deficit syndrome.

Neuropsychiatric, Psychoeducational, and Family Characteristics of 14 Juveniles Condemned to Death in the United States

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Of the 37 juveniles currently condemned to death in the United States, all of the 14 incarcerated in four states received comprehensive psychiatric, neurological, neuropsychological, and educational evaluations. Nine had major neurological impairment, seven suffered psychotic disorders antedating incarceration, seven evidenced significant organic dysfunction on neuropsychological testing, and only two had full-scale IQ scores above 90. Twelve had been brutally physically abused, and five had been sodomized by relatives. For a variety of reasons the subjects' vulnerabilities were not recognized at the time of trial or sentencing, when they could have been used for purposes of mitigation.

(Am J Psychiatry 1988; 145:584–589)

The purpose of this paper is twofold: to describe the biopsychosocial characteristics of 14 juveniles sentenced to death in the United States and to explore the implications of these findings for imposition of the death penalty on juveniles.

The execution of juveniles in America dates back to the seventeenth century when, in 1642, a child was executed for the crime of bestiality (1). Since then, 272 juveniles have been executed in the United States (2). This figure includes the execution in 1985–1986 of three boys who were condemned as juveniles but who were not executed until after they reached their majority. During our study (1986–1987), the number of juveniles awaiting execution rose from 33 to 37.

U.S. law permitting the execution of juveniles is based on English common law (3, 4). Blackstone, in his *Commentaries on the Laws of England* (5), commented, "If it appear to the court and jury that he was *doli capax,* and could discern between good and evil, he may be convicted and suffer death."

Although U.S. law regarding the responsibility of children has rested heavily on the commentaries of English jurists such as Blackstone, modifications based on case law have occurred (6). For example, in the case of *State v. Aaron* (7), in which an 11-year-old slave was accused of murdering a younger child, the 11-year-old's conviction and sentence of death were overturned by the Supreme Court of New Jersey. The presumption of innocence had not been refuted by "strong and irrefutable evidence that he had sufficient discernment to distinguish good from evil."

The outcome was quite different in the case of *Godfrey v. State* (8), in which a slave of approximately 11 years of age hacked a 4-year-old to death. Covered with blood, the accused child blamed the act on imaginary Indians. The child was sentenced to death, and in spite of clear evidence of infantile reasoning, he was executed.

We seem to have inherited a paradoxical set of traditions. We have a juvenile justice system that recognizes the emotional and intellectual immaturity of juveniles and holds them less culpable than adults; at the same time, in the case of certain kinds of serious offenses, juveniles are tried in the criminal justice system and their punishment for these offenses, including execution, is meted out as though juveniles were as responsible as adults.

Little or nothing is currently known about the mental condition and cognitive capacities of juveniles sentenced to death. Given the dearth of information regarding the biopsychosocial status of condemned juveniles, we welcomed the opportunity to conduct comprehensive assessments of approximately 40% of the 37 juveniles who are currently awaiting execution in the United States.

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METHOD

Our subjects were 14 boys who were sentenced to death for a capital offense committed before they reached age 18. The subjects comprised all the juveniles sentenced to death in four states with statutes that permit the execution of minors. The subjects were chosen because of their youth and not because of any known psychopathology. They therefore can be presumed to be representative of the juvenile death row population in general. Their ages at the time of their offenses ranged from 15 years 10 months to 17 years 10 months (mean, 16 years 6 months). Their ages at the time of their evaluations ranged from 17 years 10 months to 29 years 2 months (mean, 22 years 3 months). There were six black subjects, seven white subjects, and one Hispanic subject. Informed consent was obtained from subjects and their attorneys.

The diagnostic evaluation consisted of psychiatric, neurological, psychological, neuropsychological, educational, and EEG examinations. The psychiatric examination consisted of a semistructured interview based on an expanded version of the Bellevue Adolescent Interview Schedule. This schedule, consisting of 160 questions, was devised because no existing diagnostic instrument for children or adults dealt adequately with topics such as medical history, history of neuropsychiatric symptoms (e.g., psychomotor symptoms), characteristics of temper, or history of physical abuse. A trial of this instrument before its use in this study revealed that data obtained were appreciably more comprehensive than those elicited after a routine 2-week evaluation on an inpatient teaching service on adolescents.

Detailed neurological histories were obtained by the psychiatrist and the neurologist. Whenever histories of CNS insults were elicited, attempts were made to corroborate the histories through physical examination (e.g., scars, neurological signs), record reviews, and specialized tests (e.g., EEG). Standard neurological examinations were performed on 12 of the 14 subjects (in two cases, scheduling precluded a neurological examination). The neurologist also performed a mental status examination. Paranoid ideation was evaluated by both clinicians because of its importance in previous studies (9) and because of the subjectivity inherent in the assessment of this particular symptom. In only one case did their ratings differ, and in that case, the subject was coded as not having paranoid symptoms.

Certain other information was obtained independently by both the psychiatrist and the neurologist. Both tried to ascertain whether a child had been the victim of abuse or had been witness to extreme family violence. A subject was considered to have been physically abused if he had been punched; beaten with a stick, board, pipe, or belt buckle; or beaten other than on the buttocks with a belt or a switch. A subject was not considered to have been physically abused if he had been struck only with an open hand or beaten only on the buttocks with the leather part of a belt. A subject was considered to have been sexually abused if older persons had fondled his genitals or penetrated his anus or if he had been forced to perform sexual acts on an older person of either sex.

A neurometric quantitative EEG was performed on all subjects. For the purposes of this phase of the study, 2 minutes of artifact-free quantitative EEG data were analyzed visually in order to determine the existence of sharp waves and/or actual seizure activity. Neuropsychological testing consisted of the WAIS, Revised (10), Bender-Gestalt test (11), Rorschach Test (12), House-Tree-Person Test (13), and the Halstead-Reitan Battery of Neuropsychological Tests (14). Educational testing included the Woodcock-Johnson Psycho-Educational Battery (15), the Mini-Screen subtest from the Test of Adolescent Language (E. Prather, unpublished), the Story subtest from the Test of Written Language (16), and a speech screening test.

Findings were made available to individual attorneys if requested.

FINDINGS

Table 1 presents evidence of CNS trauma. As can be seen, eight subjects had had injuries that were severe enough to result in hospitalization, and/or indentation of the cranium (subjects 1, 2, 4, 7, 8, 12, 13, 14). For example, one subject was hit by a truck at age 4 years, was comatose for days, and was hospitalized for 11 months; another was hit by a car at age 6 years and hospitalized for 6 months.

Table 2 illustrates the neurological and EEG findings. In nine cases serious neurological abnormalities were documented, including evidence of focal brain injury (subjects 1 and 13), major neurological abnormalities such as abnormal head circumference or a positive Babinski sign (subjects 5, 10, 12), a history of grand mal seizures (subject 6), and symptoms or EEG findings strongly suggestive of a previously undiagnosed seizure disorder (subjects 2, 7, 8).

Table 3 illustrates the severe psychopathology characteristic of the 14 juveniles. As can be seen, seven of the subjects were psychotic at the time of their evaluations or had been so diagnosed in earlier childhood (subjects 1, 2, 3, 6, 9, 12, 14). An additional four subjects had histories consistent with diagnoses of severe mood disorders (subjects 5, 7, 10, 11). The three remaining subjects experienced periodic paranoid ideation, at which times they often assaulted their perceived enemies. Seven of the subjects suffered from psychiatric disturbances that were first manifested in early or middle childhood.

Table 4 presents data from selected subtests of the psychoeducational test batteries. This table illustrates that only two subjects had IQ scores above 90. Of particular importance was the finding that 10 subjects scored significantly below grade level on the concept formation subtest, and nine subjects made more than

TABLE 1. Head Injuries of 14 Juveniles Condemned to Death

Subject	Nature of Trauma	Objective Evidence
1	Automobile accident at age 12 (loss of consciousness); repeated blows to the head by father in infancy	Deep indentation of cranium behind right ear
2	Hit by truck at age 4—fractured skull, coma	11-month hospitalization
3	Fall from tree at age 11 (loss of consciousness)	Multiple scars on head
4	Shot in right temple at age 16	Indentation in right temporal area; many scars on face
5	Blow to head at age 8—amnesia for 2 weeks	No documentation
6	Fell from roof at age 10 (loss of consciousness); motorcycle accident at age 15	Multiple scars on head
7	Car accident at age 10 (loss of consciousness); hit in head with board during early childhood	Indentation of forehead
8	Fell from bunk bed at age 7; serious bicycle accident in later childhood	Indentation of cranium in center of forehead; multiple facial scars
9	Motorcycle accident in adolescence	No documentation
10	Fell from bed onto face in infancy; car accident with head injury; fell down flight of stairs in early childhood	Deviated septum from first accident; scars on chin and upper lip
11	Car accident in early childhood (possible loss of consciousness); motorcycle accident at age 17	No documentation
12	Hit by car at age 6 (loss of consciousness); fell from roof onto chin in later childhood	6-month hospitalization for first accident; scar in occipital area
13	Fell from tree at age 7; ran into car while riding bicycle at age 13	Prominent bump on right side of forehead; scar behind left ear
14	Severe bicycle accident at age 12 (loss of consciousness)—broke nose and was told he "cracked skull"	Surgery to repair nose; multiple facial scars

TABLE 2. Signs and Symptoms of Neurological Dysfunction in 14 Juveniles Condemned to Death

Subject	Subjective Symptoms	Objective Evidence
1	Lapses of fully conscious awareness; frequent, severe headaches	Suggestion of focal damage (e.g., extinguished left visual field); EEG: increased slow waves in right temporal and bilateral parieto-occipital regions, possible sharp waves; evidence of diffuse cerebral dysfunction
2	Dizzy spells, falling, confusion; multiple psychomotor symptoms	Neurologist suspects seizures; EEG attempted but data not obtained
3	Bizarre, violent behavior with memory impairment; multiple psychomotor symptoms	Neurological exam not performed; EEG: sharp waves in left temporal region
4	Lapses of awareness; migraine headaches	Normal findings on neurological exam; EEG: bilateral temporal sharp waves
5	Severe headaches	Babinski sign on right side; EEG attempted but data not obtained
6	History of grand mal seizures; multiple psychomotor symptoms	Mild left-sided weakness; bilateral unsustained clonus; EEG attempted but data not obtained
7	Multiple psychomotor symptoms	Hyperactive deep tendon reflexes; EEG: severe abnormalities in left temporal and right frontal regions
8	Occasional dizziness and lapses of awareness	Neurological exam not performed; EEG: sharp waves throughout record, especially in left temporal area
9	Episodes of dizziness	Saccadic eye movements, otherwise normal findings on neurological exam; EEG: possible sharp waves
10	Hypergraphia, micropsia; possible lapses of awareness	Unsustained bilateral ankle clonus, multiple "soft" signs; EEG: equivocal sharp waves in temporal and central regions
11	Lapses of awareness; dizzy spells; multiple psychomotor symptoms	Multiple soft signs; EEG: equivocal sharp waves in right parietal and posterior temporal regions
12	Severe headaches; impaired memory of behavior	Macrocephaly; EEG attempted but data not obtained
13	Lapses of awareness; impaired memory of behavior; frequent déjà vu	Left ankle clonus; poor rapid alternating movements on left side; "evidence of right hemisphere dysfunction"; EEG: diffusely abnormal
14	Lapses of awareness; multiple psychomotor symptoms	Normal findings on neurological exam; EEG: possible sharp activity

50 errors on the categories subtest. Both subtests are indicators of impaired abstract reasoning. The reading comprehension subtest scores of the Woodcock-Johnson Psycho-Educational Battery indicated that only three juveniles were reading at grade level. In fact, three subjects did not learn to read until their incarceration on death row.

As shown in table 5, 12 of the subjects had been

TABLE 3. Psychiatric Characteristics of 14 Juveniles Condemned to Death

Subject	Recent Psychiatric Signs and Symptoms	Childhood Indicators of Psychopathology
1	Paranoid ideation; command hallucinations; rambling, illogical speech	Severe emotional and behavioral problems since kindergarten; required special classes
2	Grandiosity, racing thoughts, insomnia; episodically paranoid; suicide attempts	Psychiatrically hospitalized age 15, diagnosed as having "organic psychosis"
3	Auditory hallucinations; paranoid ideation	None
4	Questionable paranoid ideation	None
5	Severely depressed and suicidal during interview; episodes of racing thoughts and insomnia	Recurrent depressions since childhood; suicide attempt at age 11
6	Auditory and visual hallucinations during interview; paranoid ideation	Visual and auditory hallucinations beginning at age 9
7	Auditory hallucinations; manic episodes and depressive episodes	Psychiatric symptoms requiring evaluation at age 8
8	Paranoid ideation	None
9	Paranoid ideation; auditory hallucinations	None
10	Suggestion of bipolar mood disorder, insomnia, racing thoughts, hypergraphia, hyperactivity	Psychiatric treatment at age 12 for compulsive sexually deviant behaviors
11	Paranoid misperceptions; one episode of auditory hallucinations; depressive and euphoric periods	Depressive symptoms since early childhood
12	Illogical; delusional; paranoid; inappropriate smiling (paranoid schizophrenic)	Multiple psychiatric evaluations and treatments since age 6
13	Questionable paranoid ideation	Drug abuse since age 8; alcohol abuse since age 10
14	Visual and auditory hallucinations; bizarre behavior (e.g., drinking blood, sticking tacks in head)	Auditory hallucinations since age 6

TABLE 4. Neuropsychiatric and Psychoeducational Scores of 14 Juveniles Condemned to Death

	WAIS-R IQ			Halstead-Reitan Battery			Woodcock-Johnson Battery		
Subject	Verbal	Performance	Full-Scale	Categories (errors)[a]	Tactile Performance (minutes)[b]	Impairment Index[c]	Reading Comprehension (grade equivalent)	Calculation (grade equivalent)	Concept Formation Score
1	67	63	64	113	37.0	1.0	2.3	3.0	1.0[d]
2	85	84	85	57	9.4	0.4	7.6	3.3	5.8[d]
3	76	82	77	57	10.8	0.7	6.6	7.5	1.0[d]
4	75	76	74	96	23.3	0.7	5.8	7.5	2.2[d]
5	88	88	86	90	9.5	0.6	12.9	5.0	12.8
6	80	87	82	93	27.3	0.9	10.6	6.6	8.6
7	84	71	77	93	25.0	0.7	5.6	5.0	4.6[d]
8	75	85	77	66	18.6	0.7	8.6	5.3	3.0[d]
9	84	85	83	38	21.6	0.7	8.6	8.0	5.8[d]
10	112	99	106	15	8.4	0.1	12.9	12.9	7.1[d]
11	68	91	81	23	12.7	0.4	1.1	6.6	3.6[d]
12	71	77	73	91	15.6	0.5	2.0	2.6	1.0[d]
13	86	94	88	11	6.4	0.0	9.5	6.2	10.8
14	115	125	121	19	8.9	0.0	12.9	12.9	19.9

[a] More than 50 errors indicates significant brain dysfunction.
[b] More than 15 minutes indicates significant brain dysfunction.
[c] An overall index of 0.7 or greater indicates brain damage.
[d] Subject functions significantly below his appropriate grade level.

brutally, physically abused and five had been sodomized by older male relatives. Therefore, not only did older family members fail to protect these adolescents, but they also often used the subjects to vent their rages and to satisfy their sexual appetites. Alcoholism, drug abuse, psychiatric treatment, and psychiatric hospitalization were prevalent in the histories of the parents.

DISCUSSION

Our data, based on evaluations of approximately 40% of the juvenile death row population, indicate that juveniles condemned to death in the United States are multiply handicapped. They tend to have suffered serious CNS injuries, to have suffered since early childhood from a multiplicity of psychotic symptoms, and to have been physically and sexually abused.

Theoretically, all of the vulnerabilities described—neurological impairment, psychiatric illness, cognitive deficits, and parental abusiveness—were potentially mitigating factors that, coupled with youthfulness, would have argued against the imposition of a death sentence. Unfortunately, these cognitively handicapped juveniles had little if any recognition of the existence of these vulnerabilities, much less of their

TABLE 5. Physical and Sexual Abuse, Family Violence, and Family Psychiatric Illness of 14 Juveniles Condemned to Death

Subject	Physical Abuse	Sexual Abuse	Family Violence and Psychiatric Illness
1	Beaten by father, mother, stepfather; blows to head	None	Violence between parents; father alcoholic; mother alcoholic and drug abuser
2	Hit in head with hammer by stepfather	Sodomized by stepfather and grandfather throughout childhood	Violence between parents; mother psychiatrically hospitalized
3	Placed in children's shelter in early childhood	None	Violence between parents; mother medicated for "nerves"
4	Whipped all over body by stepfather; mother broke plate over subject's head	None	Violence between parents
5	Punched by father; beaten on legs and buttocks by mother	None	Violence between parents
6	Seated on hot burner by stepfather (scars on buttocks)	Sodomized by stepfather and his friends; possible sexual abuse by mother and brother	Father beat mother during pregnancy; mother had several "nervous breakdowns"
7	Punched and hit in head with board by father (broke teeth)	None	Violence between parents; mother had multiple hospitalizations and seizures
8	Beaten by father with bullwhips and boards	None	Violence between parents; father possibly alcoholic
9	Beaten by stepfather all over body with cords	None	Siblings beat up stepfather for his mistreatment of subject
10	None	None	None
11	Beaten by mother, father, grandmother	Sodomized by uncle and male cousin from age 5 to 11; sexually abused by older female cousin at age 4	Violence between parents; father alcoholic and psychotic; both parents take medication for "nerves"
12	Beaten by father and mother, sometimes in the face	None	Father alcoholic; mother depressed and alcoholic
13	Beaten and stomped by older brother; whipped by mother; kicked in head by relative	Sodomized by older cousin in early childhood; sexual assault attempted by male relative	Extreme violence with weapons by several family members
14	Beaten from infancy by father, mother, and grandfather	Sodomized by family member and family friend in childhood	Stepfather extraordinarily violent (e.g., preferred "hunting men" to animals); mother medicated for "nerves"

relevance to issues of mitigation. In fact, they almost uniformly tried to hide evidence of cognitive deficits and psychotic symptoms. They frequently told examiners, "I'm not crazy" or "I'm not a retard." It required comprehensive, specialized evaluations to obtain accurate clinical information.

Similarly, these juveniles were ashamed of their parents' brutality toward them and tried to conceal or minimize it. Only painstaking, lengthy interviews, inquiring in detail about injuries, the origin of visible scars, and the existence of "scars I can't see" revealed the extent to which they had been victimized. Suffice it to say that a history of sexual abuse was even more difficult to elicit. Thus, these juveniles systematically concealed factors in their lives that were most likely to mitigate a death sentence.

Unfortunately, the parents, who should have assisted in their children's defenses, were inadequate to this task by virtue of their own psychopathology. They also had vested interests in concealing their own abusiveness, misconduct that would have constituted mitigating circumstances. In fact, we have found that in several adult and juvenile capital cases, family members have requested that histories of abuse be minimized, have cooperated with the prosecution, have testified against their own family members, or have urged the judge to impose a death sentence.

Conceivably, the juveniles' lawyers might have been relied upon to unearth and make use of the kinds of clinical data described in this paper. Such was not the case. The time and expertise required to document the necessary clinical information were not available. Furthermore, the attorneys' alliances were often divided between the juveniles and their families. In fact, on several occasions, attorneys who chose to make use of our evaluations requested that we conceal or minimize parental physical and sexual abuse to spare the family any embarrassment.

Thus, some of the very factors that led to the juveniles' aggression in the first place also contributed to an inadequate defense during the sentencing phase of their trials. Brain damage, paranoid ideation, physical abuse, and sexual abuse, all relevant to issues of mitigation, were either overlooked or deliberately concealed. Of note, in only five cases were any pretrial evaluations performed at all. These tended to be perfunctory and provided inadequate and inaccurate information regarding the adolescents' neuropsychiatric and cognitive functioning.

Adolescence is well recognized to be a time of physiological and psychological change and stress. Normal adolescents are distinguished from adults by their intensity of feeling, immature judgment, and impulsiveness. Our data indicate that, above and beyond these maturational stresses, homicidal adolescents sentenced to death have had to cope with brain dysfunction, cognitive limitations, severe psychopathology, and violent, abusive households.

At this time the clinical and legal services necessary to try to uncover these vulnerabilities are routinely unavailable to this population of juveniles. Moreover, even when such services are made available, the very family members on whom these juveniles must rely to assist in their defenses often collude with each other, the juvenile, and the attorney to minimize or conceal entirely the violence and abusiveness experienced in the home. Thus juveniles accused of a capital offense are uniquely vulnerable; they lack the maturity or insight to recognize the importance of psychiatric or neurological symptoms to their defense; and they are dependent on family for assistance in a way that adult offenders are not. Our data shed light on some of the special difficulties encountered when adolescents are treated as though they were as responsible as adults and are condemned to death.

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A Pilot Study of Treatment of Social Phobia With Alprazolam

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Fourteen patients with DSM-III *social phobia were treated with alprazolam in an open study. Multiple measures of symptoms and disability showed significant improvement. The symptoms improved during the first and second weeks, and disability improved at 3 weeks and beyond. After medication withdrawal the symptom and disability measures were no longer significantly different from those at baseline.*

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Social phobia, although long recognized by researchers, has until recently been the object of relatively few pharmacologic treatment trials. This neglect may be due in part to the fact that it has only recently been recognized as distinct from other anxiety disorders. In 1970 Marks (1) divided the anxiety disorders into three categories—agoraphobia, simple phobia, and social phobias. He defined social phobias as fears triggered only by situations involving other people and as fears of social humiliation. (A definition along these lines was incorporated into *DSM-III.*) Studies of the demographic characteristics of patients with social phobia (2, 3) revealed that it has an earlier onset and a higher male-to-female ratio than agoraphobia. One study (4) demonstrated a lower prevalence of panic attacks in response to lactate infusion in patients with social phobia than in those with panic disorder. In 1985, in a comprehensive review of the clinical, demographic, and biochemical literature, Liebowitz et al. (5) concluded that the weight of the evidence was in favor of the existence of social phobia as a distinct entity.

Although some pharmacologic trials have been aimed at alleviating specific anxiety symptoms (these were reviewed by Liebowitz et al.), there have been relatively few involving well-defined samples of patients with social phobia. The treatment studies using related samples include the double-blind study of Falloon et al. (6), who added either propranolol or placebo to social skills training for 16 patients with social phobia. They found that although social skills training improved target symptoms, there was no significant difference between placebo and propranolol. Two other small studies (one with 16 and one with 10 subjects) achieved positive results with propranolol (7) and atenolol (8), respectively, which are both beta blockers. The first study was double blind. There have been two reports of treatment of social phobia with phenelzine. One was a case report of the successful treatment of one patient (9), and the other was a report from an open trial involving 11 patients with social phobia (10). In the open trial, seven patients showed marked improvement and four showed moderate benefit. The only reported trial of benzodiazepines (lorazepam versus diazepam) was the treatment of six phobic patients (11). From the description given, only two appeared to definitely have specific symptoms of social phobia. One of these improved mildly while taking lorazepam, and the other improved mildly with diazepam.

Finding an effective treatment for this disorder is important because it can cause significant disability (5) and is relatively prevalent. Myers et al. (12) estimated that the 6-month prevalence in a community sample was between 1% and 2%. We believe that ours is the first study of alprazolam for the treatment of social phobia. It was a pilot study designed to assess the feasibility of further research.

METHOD

Subjects were recruited through advertising to take part in a treatment study of social phobia. The subjects were initially screened over the telephone and then in interviews with a physician. It was required that each patient be between 18 and 65 years old, have *DSM-III* social phobia as diagnosed with the Structured Clinical Interview for *DSM-III* (SCID) (13), and if female, ensure that she would not become pregnant during the study. It was also required that each subject be experiencing at least one social phobic situation a week, take no antianxiety medications besides the study medication during the course of the study, and actively

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enter feared situations during the course of the study. Patients were excluded if they had psychotic illnesses, organic brain syndromes, mental retardation, panic disorder, drug or alcohol abuse in the last year, or a major depressive disorder that preceded or dominated the clinical picture. Before entering the study each patient gave written informed consent.

Axis I diagnoses were diagnosed with the SCID I (13). This instrument, which is in wide clinical use, was designed to be given by a skilled clinician and gives *DSM-III* diagnoses. The Hamilton Rating Scales for Anxiety and Depression were used to measure state anxiety and depression, respectively.

A number of scales were used to measure social avoidance symptoms. The Social Phobic Disorders Rating Form (available from M.R. Liebowitz, New York State Psychiatric Institute, New York) measures each of four aspects of social phobia (overall severity, overall functional impairment, phobic avoidance, and anticipatory anxiety) on a 7-point scale. It is completed by a physician. The Social Anxiety Scale (available from M.R. Liebowitz) is a self-report that measures both performance anxiety and social anxiety. The Fear Questionnaire (14) and the Fear of Negative Evaluation Questionnaire (15), which are self-report measures, were also used. In addition, the Willoughby Personality Inventory (16), a self-report measure that has a strong relationship to social fears, was given. These scales have all been successfully used previously in studies of patients with social fears (Liebowitz, personal communication). In addition, physician and patient ratings of global improvement and the patient-rated Sheehan Disability Scale were given (available from Upjohn Company, Kalamazoo, Mich.).

After successfully passing screening by a psychiatrist (J.R. or W.Y.) who administered the SCID I, each enrolled patient spent one week without any anti-anxiety medication. At the end of the week, baseline measures were taken and the patient began taking alprazolam. The dose was 1 mg/day initially and could be raised, as clinically indicated, to 10 mg/day. The dose was increased until either all social phobic symptoms disappeared or side effects precluded further increases in dose. The treatment phase lasted 8 weeks, and the patient was seen at the end of weeks 1, 2, 3, 4, 6, and 8. After the end of week 8, the patient's alprazolam dose was tapered off. After 1 week with no medication, the patient was retested.

All measures were given at every visit, except the SCID I, which was given only at screening, and the Hamilton depression scale, which was given at baseline, week 4, and week 8. A patient had to complete 3 weeks of treatment and encounter the feared social situation to complete the study.

The alprazolam dose was tapered by one of two methods. The first was to reduce the alprazolam dose 1 mg/day every 3 days until it reached 2 mg/day. At that point the dose was reduced 0.5 mg/day every 3 days until the medication was stopped. The second method was to replace the alprazolam dose with a dose of diazepam and to reduce the diazepam dose 10% a day. The initial starting dose of diazepam was usually a milligram-for-milligram substitution, e.g., if a patient was taking 1 mg of alprazolam three times a day, he or she was switched to 3 mg/day of diazepam. Usually the diazepam dose was given at bedtime. However, this was highly flexible, and the patient could call the physician during the first day or two if there was any problem. Often the initial dose was increased, decreased, or changed to divided doses. The method of tapering used was at the discretion of the physician who saw the patient in the study.

As the data were normally distributed and otherwise appropriate, analysis of variance for repeated measures was used to analyze the variables at baseline, weeks 1, 2, 3, 4, 6, 8, and after tapering to determine whether significant change over time occurred. Post hoc comparisons of the weekly scores were performed by means of the Tukey method to determine whether the score at week 8 of treatment differed from that at baseline and whether the baseline score differed from the score after drug tapering or in the week when maximum therapeutic effectiveness was reached. This type of analysis enabled us to perform only one statistical test per measure and thereby reduce type 1 error (positive results secondary to multiple statistical tests). Because of the small sample size, analyses by age and sex were not performed.

RESULTS

Seventeen patients were recruited into the study. Of these, one did not return after his baseline visit and one developed a major depression that required specific treatment 2 weeks into alprazolam treatment and had to be withdrawn from the study. A third patient completed 3 weeks of treatment but refused to enter situations that caused him to be socially fearful. The 14 remaining patients, on which our analysis was based, all completed 8 weeks of treatment and returned after the alprazolam had been tapered. This group consisted of nine men and five women and their mean±SD age was 44.0±14.1 years. In addition to social phobia, which all the patients had, some patients had the following axis I diagnoses: major depressive episode (N=6), dysthymia (N=1), and simple phobia (N=5). Nine subjects were married, one was not currently married, and four had never married. There were no significant differences in age, marital status, or axis I disorders between the men and women. By week 8 the subjects were taking a mean±SD weekly dose of 20.2±9.8 mg of alprazolam, or 2.9 mg/day. The range of doses was 1–7 mg/day, and 11 patients were taking 3 mg/day or less.

Table 1 gives the mean scores on the symptom and disability measures for baseline, for treatment weeks 1, 2, 3, 4, 6, and 8, and for the week after the end of the drug tapering. In every instance (whether significant or not), the trend was in the expected direction—toward

TABLE 1. Symptom and Disability Scores of 14 Patients With Social Phobia Who Received Alprazolam

	Score											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6	
Instrument	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Symptom measures												
Hamilton anxiety scale	13.7	4.4	4.4[c]	1.9	3.4[c]	1.8	4.1[c]	2.0	3.7[c]	1.8	3.6[c]	2.1
Hamilton depression scale	9.1	4.4	—	—	—	—	—	—	3.1[c]	2.9	—	—
Global improvement												
Physician rating	4.1	4.8	2.4[c]	2.6	1.7[c]	1.6	2.1[c]	2.0	1.7[c]	1.9	1.9[c]	1.8
Patient rating	3.8	1.3	2.1[c]	0.8	2.4[c]	0.9	2.8[c]	0.7	2.5[c]	0.9	2.8[c]	0.8
Social Phobic Disorders Rating Form												
Severity	4.0	0.6	2.6[c]	0.9	2.2[c]	0.6	2.4[c]	1.1	1.8[c]	1.0	1.9[c]	0.7
Phobic avoidance	4.1	1.2	2.1[c]	0.6	2.0[c]	0.9	2.3[c]	1.0	1.9[c]	0.7	1.4[c]	0.8
Anticipatory anxiety	3.8	1.0	2.7[c]	0.8	2.6[c]	0.7	1.9[c]	0.6	2.1[c]	0.6	2.3[c]	0.9
Social Anxiety Scale												
Performance anxiety	19.4	7.6	12.4	5.5	8.1[c]	3.2	9.9[c]	3.5	8.3[c]	3.9	8.5[c]	3.8
Social anxiety	15.1	9.3	9.6	5.1	6.0[c]	3.1	6.7[c]	3.4	4.5[c]	3.0	4.9[c]	2.8
Fear Questionnaire	42.6	25.1	31.7	16.2	20.3[c]	10.9	19.4[c]	11.0	16.9[c]	9.1	16.1[c]	8.7
Willoughby Personality Inventory	52.5	18.5	41.7	19.1	35.6	16.2	37.4	16.0	33.2	14.8	32.4	17.0
Fear of Negative Evaluation Questionnaire	22.4	7.3	16.7	7.1	15.5	7.5	16.9	5.9	14.7	5.7	15.6	6.8
Disablity measures												
Social Phobic Disorders Rating Form, functional impairment scale	3.2	1.3	1.9[c]	1.1	1.4[c]	0.8	1.6[c]	0.7	1.4[c]	0.7	1.2[c]	0.8
Sheehan Disability Scale												
Work	3.6	2.6	2.3	1.1	1.8	1.1	1.7	0.7	1.4[c]	0.5	1.3[c]	0.6
Leisure	5.5	2.9	3.3	1.4	3.1	1.0	2.7[c]	1.1	1.6[c]	0.9	2.1[c]	0.9
Family	2.2	2.0	1.8	1.6	1.4	1.4	0.9	1.2	0.9	0.9	1.2	0.8
Overall	3.6	1.0	2.6	0.9	3.1	0.9	2.5	0.8	2.4	0.9	2.4	0.7

[a] In each case where there was a significant overall finding, the score at baseline was significantly different from that at week 8 of treatment but not significantly different from that after drug tapering. This was determined by using Tukey's post hoc test with the significance level set at $p<0.05$. The Tukey test was also used to determine the week in which the maximum treatment effect was first reached.

[b] The first point at which the score was significantly below the baseline score but not significantly different from any subsequent treatment score. For example, if at week 2 the score was significantly lower than at baseline for the first time and if the scores at weeks 3, 4, 6, and 8 were not significantly different from the week 2 score, then week 2 was the first week of maximum treatment effect.

[c] Significantly different from baseline score.

less severe symptoms or less disability over the 8 weeks of treatment. In every instance where the overall change was significant, the score at week 8 was significantly lower than at baseline. In no case was the score after tapering significantly different from that at baseline, although the absolute scores tended to be a bit lower.

The results were also impressive from a clinical point of view. On the week 8 physician rating of clinical global improvement, 10 patients scored 1, the highest possible score (indicating very much improvement), and the remaining four scored the next highest, or 2 (indicating much improvement). On the physician-scored measure of social phobic symptom severity, 11 patients had a 50% or greater reduction from baseline at week 8. The three remaining patients had at least a 20% reduction in symptoms.

Side effects were few and largely limited to sedation or disinhibition. When encountered, these side effects all responded to a reduction in dose. No disinhibition side effects resulted in work, family, or social problems. They were merely reported to us and corrected by dose adjustment. One patient experienced sedation that interfered with his work. Although he felt there was no change in his performance, he was accused of being sleepy at his job. He requested and received a letter to his employer explaining the medication and its side effects. The same accusation had been made about him at a previous time, before he was in our study or taking medication. No difficulties were encountered in the tapering phase of the project.

DISCUSSION

Many behavioral and medical treatments have both immediate and delayed effects. A symptom that responds immediately to pharmacological treatment may have a high chance of stemming from an underlying biological vulnerability, and one that responds to repeated environmental exposures after that biological vulnerability is removed may be an overlying trait

TABLE 1 (continued)

Score							
Week 8		1 Week After End of Drug Tapering		Overall Significance[a]			First Week of Maximum Treatment Effect[b]
Mean	SD	Mean	SD	F	df	p	
3.4^c	2.0	10.2	8.0	13.9	1, 7	0.00001	1
2.5^c	2.3	—	—	19.1	1, 2	0.00001	4
1.9^c	2.0	3.1	3.1	13.1	1, 7	0.00001	1
2.5^c	0.9	4.8	1.5	6.7	1, 7	0.00001	1
1.9^c	0.6	3.3	1.3	10.5	1, 7	0.00001	1
1.6^c	0.6	2.8	1.3	10.4	1, 7	0.00001	1
1.8^c	1.0	3.7	0.8	8.7	1, 7	0.00001	1
6.8^c	2.4	13.7	7.3	4.9	1, 7	0.0001	2
3.3^c	2.9	8.2	4.7	5.6	1, 7	0.00001	2
13.4^c	7.2	23.3	16.9	5.7	1, 7	0.00001	2
26.9^c	12.1	40.1	19.1	2.6	1, 7	0.02	8
12.0	5.1	19.7	9.9	1.5	1, 7	n.s.	
1.3^c	0.9	1.7	1.1	6.7	1, 7	0.00001	1
0.9^c	0.5	2.6	2.2	3.5	1, 7	0.002	4
1.4^c	0.6	4.1	3.1	5.1	1, 7	0.0001	3
0.7	0.6	0.9	1.0	1.9	1, 7	n.s.	
2.0	0.6	2.9	1.0	1.5	1, 7	n.s.	

effect. In this study, the scores on practically all of our straightforward symptom measures dropped markedly in the first week or two of treatment. The disability measures, which might in this case also reflect some learning and indicate overlying traits, tended to improve at week 3 or 4; the scores on the Sheehan family and overall scales did not improve significantly, but the trends were in the expected direction. The score on the Fear of Negative Evaluation Questionnaire, which appears to deal with cognitive constructs, did not change significantly, although it did improve, and the score on the Willoughby Personality Inventory, a personality measure, did not change significantly until week 8. The functional impairment rating on the Social Phobic Disorders Rating Form was significantly improved at week 1, but this measure most likely represents the rating physician's reliance on symptoms of the disorder in addition to disability.

If some of the improvement seen was secondary to learning through exposure, we might expect some of the values after drug tapering to be significantly below the baseline values. Although most of the posttapering values were lower than the baseline values, they were not significantly so. The failure to reach significance could be due to several factors. First, there may not have been enough time for the learning to take place. Second, the return of symptoms after withdrawal of medication may have temporarily obscured the learning effect. Third, learning may not be as effective if the underlying biologic vulnerability is restored. Longer trials of medication and follow-up of treated patients after medication trials are necessary to answer this question. Possibly medication plus cognitive-behavioral psychotherapy might most effectively address both components of the illness. It should be remembered that alprazolam is a potentially habit-forming drug, and caution should be used in prescribing it over the long term, especially in patients with histories of alcohol or substance abuse.

The major weaknesses of this study were its open design and the lack of a control group. This was a pilot study and was intended to provide preliminary information about potential effectiveness, dosage, and side effects for use in designing a double-blind study. As a result, it cannot be said how much the placebo effect influenced the outcome of this study. The patients knew when their medication doses were being tapered. Double-blind studies must be performed to answer this question.

An interesting line of inquiry suggested by this study is the possible investigation of the treatment of avoidant personality disorder. Social phobia and avoidant personality disorder appear to differ only in degree. There is already one report of a case of combined social phobia and avoidant personality disorder that was treated with a monoamine oxidase inhibitor (10). Should alprazolam prove effective in the treatment of social phobia, a trial for avoidant personality disorder would certainly be reasonable. At present there is too little empirical evidence to say that alprazolam would be effective for avoidant personality disorder; however, it might be used clinically on a case-by-case basis.

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Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Jan. 8 and Feb. 26, 1988.

Richard M. Aderhold
J. Armstrong, Jr.
Samuel Atkin
Irma Bache
R. Stephen Barnes
Stuart Bergsma
Wilfred Bloomberg
Edward Blumberg
John Bostock
William W. Bourke
Spencer H. Brown
Neil R. Burch
Carol Lynne Burgoyne
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Charlotte V. Delhaes
Sidney Elpern
Imogene Fairchild
Hannah W. Fehler
Samuel Feldman
Henry M. Fox
Paul Vollrad Gustafson
Thomas P. Hackett
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Bernard H. Hall
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Donald McKinley
Horace G. Miller
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Emily Mumford
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Kenneth Soddy
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Jean A. Thompson
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William D. Voorhees, Jr.
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Sol S. Winsten
George P. Wyman

Use of Laboratory Tests to Monitor Heavy Drinking by Alcoholic Men Discharged From a Treatment Program

Michael Irwin, M.D., Steve Baird, M.D., Tom L. Smith, Ph.D., and Marc Schuckit, M.D.

Changes in blood test values from the time of discharge from an alcohol treatment program to 3-month follow-up were studied in two consecutive series of alcoholic men. The parallel combination of a percent increase in γ-glutamyltransferase (GGT) of ≥20%, in aspartate aminotransferase (SGOT) of ≥40%, and in alanine aminotransferase (SGPT) of ≥20% over discharge values was developed as a rule and then cross-validated to identify those alcoholic men who had resumed drinking at follow-up. Serial determination of these three test values in combination can be used to distinguish recovering alcoholics who remain abstinent from those who resume drinking.

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The clinical course of alcoholism is a fluctuating one, marked by periods of drinking problems that last from months to years and alternate periods of abstinence (1). Relatively short periods of nonproblem drinking often give way to escalation of alcohol intake, development of problems, and a beginning of the cycle over again (2, 3).

Early identification of the actively drinking alcoholic is the first step in confrontation and the institution of treatment, before risks of morbidity and mortality increase (4). During aftercare programs that follow rehabilitation efforts, identification of the alcoholic who has resumed heavy drinking could, at least in theory, help abort the spiral of drinking and associated problems before physical and behavioral reinforcers make abstinence difficult (4).

Unfortunately, early recognition of the alcoholic who has resumed drinking after treatment is not easy (3, 5); additional help in identifying a return to heavy drinking might be provided through observation of changes in blood test values. Among abstinent persons who subsequently resume drinking, it is likely that clinical laboratory values will increase above their usual abstinence levels. Heavy alcohol intake has been associated with elevated values on several widely used tests, including γ-glutamyltransferase (GGT) (6) and standard liver injury tests such as aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) (7, 8).

While cross-sectional studies have found that abnormally elevated values of these markers, alone or in combination with results of other blood tests, can help classify alcoholic versus nonalcoholic patients (8–10) and identify persons who are consuming large amounts of alcohol (10), this dichotomous approach—abnormal versus normal—is not a sensitive indicator of change in the clinical condition of a patient. Increases in test values must be quite large to exceed the hospital's "normal" range, which is based on the values that are found in 95% of the clinically well population.

Another approach is to evaluate changes over time in blood test results, including increases within the normal range that are associated with active drinking. This study examines the relationship beween changes in several blood markers and a return to drinking by alcoholic men after treatment. We hypothesized that recovering alcoholics who resume drinking will show increases in several laboratory test values over the levels of these markers during abstinence and that these changes in test values might be used to distinguish recovering alcoholics who have been recently drinking from those who have remained abstinent.

METHOD

The data presented here were generated in two stages at the San Diego VA Clinical Center for Research on Alcoholism. Stage 1 consisted of a sample of 53 alcoholic men (mean±SD age=44.9±10.7 years) for whom changes in blood test values were observed from the time of their discharge from the alcohol treatment program (after 4 weeks of abstinence) to follow-up 3 months later. These data were used to generate a rule for deciding whether a subject had returned to drinking. In stage 2, to test the validity of these results, we applied our decision rule to a second

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TABLE 1. Laboratory Test Values at Follow-Up and Percent Change From Values at Discharge of Alcoholic Men Who Abstained (N=42) or Resumed Drinking (N=11), Stage 1

	Follow-Up Value							Percent Change in Value From Discharge to Follow-Up						
	Abstainers		Drinkers		Analysis			Abstainers		Drinkers		Analysis		
Laboratory Test	Mean	SD	Mean	SD	t	df	p	Mean	SD	Mean	SD	t	df	p
GGT (42.1±40.1 U/liter)[a]	20.8	16.2	110.0	100.4	2.9	10.1	<0.02	−33	27	170	260	2.5	10.1	<0.03
SGOT (20.2±8.4 Karmen U/ml)[a]	19.4	6.9	40.6	27.3	2.6	10.3	<0.03	−8	27	130	140	3.1	10.3	<0.02
SGPT (25.6±17.4 Karmen U/ml)[a]	19.4	10.5	45.5	35.0	2.4	10.5	<0.03	−26	24	110	160	2.9	10.1	<0.02

[a] Number in parentheses is the mean±SD value for the stage 1 sample at discharge.

group of 82 alcoholic men from the same program (mean±SD age=46.3±11.0 years).

At intake into the treatment program, the patient and at least one resource person were interviewed to document the diagnosis of alcohol abuse/dependence according to the criteria of *DSM-III*. Of the 221 men admitted to the program over the course of the study, 56 were excluded from the study because they had secondary alcoholism, having met the *DSM-III* criteria for another major psychiatric disorder before the onset of alcoholism (3, 11). We also excluded from the sample another five patients who had overt liver disease, including cirrhosis or hepatic encephalopathy, two patients who were taking medications known to induce production of GGT (i.e., phenytoin, barbiturates, carbamazepine) (12), and six patients who drank alcohol during the treatment program itself. Thus, the 135 men described here represent 89% of the 152 eligible individuals and include only those for whom all discharge and follow-up blood tests and interviews were complete.

Follow-up data were gathered 3 months after discharge from the alcohol treatment program through face-to-face interviews with the patient and at least one resource person as well as review of hospital records. These data included history of alcohol consumption, symptoms of tolerance and dependence, any recurrence of alcohol-related life problems, and drug and medication histories. When conflicting information relevant to classifying a subject as an active drinker was obtained, as was the case for one individual in stage 1 and three subjects in stage 2, data reflecting the worst case history were used. Blood samples were obtained before the patients were interviewed, and the research assistants who administered the interviews were blind to the results of the laboratory tests.

For the purpose of this report, active drinkers were defined as those alcoholic men who had resumed drinking during the follow-up interval and had been drinking during the 14 days before testing. In stage 1, these drinkers (N=11) consumed a mean±SD of 6.6±8.4 drinks per day(range=4–30) (one drink=1 oz. of absolute alcohol) in the 2 weeks before follow-up; they had had their most recent drink 2.0±2.4 days before testing. In stage 2, the drinkers (N=19) consumed a mean±SD of 6.1±5.4 drinks per day (range=4–16) and had used alcohol 3.3±3.2 days before testing. The abstainers included the men who were abstinent throughout the 3 months before follow-up as well as five subjects in stage 1 who had drunk 39.2±27.2 days before testing and eight subjects in stage 2 who last drank 36.1±37.5 days before follow-up.

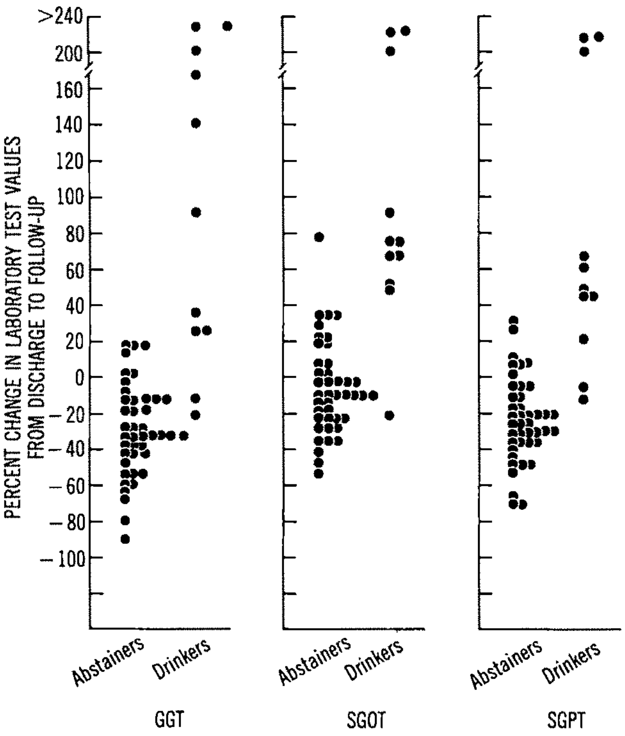
Fasting morning blood samples were collected, and serum was prepared within several hours for analysis that day. For GGT assays (13), the Abbott VP instrument and Abbott L-glutamyl-*p*-nitroamilide were used. Chemistry assays of SGOT, SGPT, globulin, alkaline phosphatase, lactic dehydrogenase, bilirubin, uric acid, albumin, total protein, cholesterol, and triglycerides were performed with a Hitachi 737 analyzer.

Percent change in test values for each individual was calculated on the basis of the difference between the discharge value and the follow-up value. Group differences in follow-up values and mean percent change from discharge to follow-up were analyzed by two-tailed t tests with separate variance estimates. The relationship between alcohol consumption and percent change of the biochemical variables was tested by the Kendall tau correlation procedure.

RESULTS

For the 53 men in stage 1, the laboratory test values at discharge were similar in the two eventual outcome groups. For three of the blood tests, GGT, SGOT, and SGPT, the drinkers (N=11) had greater mean values at follow-up and demonstrated greater mean percent increases from discharge to follow-up than the abstainers (N=42) (table 1). In comparison, other laboratory test values were either not significantly different for the two groups at follow-up (i.e., bilirubin, uric acid, albumin, total protein, cholesterol, and triglycerides) or showed mean percent increases in both the drinkers and the abstainers (i.e., lactic dehydrogenase, globulin, and alkaline phosphatase). At follow-up, alcohol consumption, as measured by number of drinks per drinking day during the preceding 2 weeks, was significantly correlated with the percent increase over discharge values of GGT ($r=0.67$, df=52, $p<0.001$), SGOT ($r=0.66$, df=52, $p<0.001$), and SGPT ($r=0.63$, df=52, $p<0.001$) but not with changes in the other laboratory test values.

FIGURE 1. Percent Change From Discharge to 3-Month Follow-Up in GGT, SGOT, and SGPT Values of Alcoholic Men Who Abstained (N=42) or Resumed Drinking (N=11), Stage 1



These data indicate that increases in some test values—particularly those of GGT, SGOT, and SGPT—over the values recorded during abstinence are associated with a return to drinking by alcoholic men after treatment. To evaluate the potential use of changes in blood test values to distinguish individuals who are drinkers from those who are abstainers, we constructed scatterplots of percent changes for the various blood tests in stage 1 and compared the distribution of percent changes for the drinkers with that for the abstainers. Plots of percent change in GGT, SGOT, and SGPT values, all of which had increased significantly more in drinkers than in abstainers, demonstrated little overlap between the two outcome groups in stage 1 (figure 1). In contrast, plots of percent change in the other laboratory test values, which were either not significantly different for the two outcome groups or showed increases in both groups, demonstrated considerable overlap between the groups and were not useful in distinguishing drinkers from abstainers (data not shown).

The different distributions of percent change in GGT, SGOT, and SGPT values in the drinkers and the abstainers of stage 1 suggested that specific cutoff points could be selected for each of these three blood tests to optimally classify subjects by drinking status. For example, in the three scatterplots of figure 1, percent change cutoff points of GGT at ≥20%, SGOT at ≥40%, and SGPT at ≥20% appeared indicative of a return to heavy drinking.

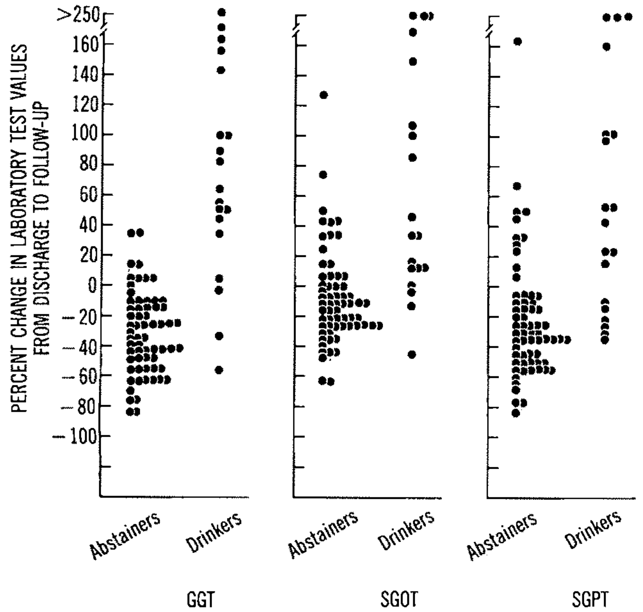
TABLE 2. Identification of Heavy Drinkers by Use of Percent Increase Cutoff Points for GGT, SGOT, or SGPT Values

Percent Increase in Laboratory Value	Sensitivity (%)	Specificity (%)
GGT≥20%		
Stage 1	82	100
Stage 2	79	97
SGOT≥40%		
Stage 1	91	97
Stage 2	47	90
SGPT≥20%		
Stage 1	80	95
Stage 2	67	82
GGT, SGOT, or SGPT increase in parallel combination		
Stage 1	100	92
Stage 2	100	82

To test the usefulness of these cutoff points in distinguishing men who have been recently drinking from those who are abstinent, the specific percent increases in GGT, SGOT, *or* SGPT values were applied separately and in parallel combination to the sample in stage 1. Parallel combination (14) involves the use of two or more tests together in an "or" combination to identify disease; for example, when looked at together, an increase in the GGT *or* SGOT value is used to identify active drinking, which contrasts with the use of these variables as single blood tests applied separately. Subjects with positive results (i.e., increases above the cutoff points) in either GGT, SGOT, or SGPT values are identified as drinkers. Table 2 summarizes the ability of GGT at ≥20%, SGOT at ≥40%, and SGPT at ≥20% singly and in combination to identify alcoholic men who had resumed drinking at follow-up. "Sensitivity" reflects the rate at which the test cutoff point identifies true positives among the drinkers, while "specificity" indicates the likelihood of identifying true negatives in the abstainers. In stage 1, these cutoff points were used separately to identify 80% or more of the drinkers in the group. A parallel combination of these percent increase cutoff points involving GGT, SGOT, *or* SGPT improved the accurate identification of drinkers to 100% while maintaining a low false-positive rate (<10%) (table 2).

In the second series of 82 additional subjects (stage 2), this decision rule was prospectively applied and its accuracy was cross-validated. The scatterplots of percent change in GGT, SGOT, and SGPT values obtained in stage 2 are shown in figure 2. The cutoff points for GGT, SGOT, and SGPT separately and in combination were comparable but not as accurate in detecting drinking in stage 2 as they were in stage 1 (table 2). While the parallel combination involving GGT, SGOT, *or* SGPT remained highly sensitive (>95%) and specific (82%), it is logical that stage 1 values, which defined the cutoff points, would show better results than those which were found in the new group of subjects in stage 2.

FIGURE 2. Percent Change From Discharge to 3-Month Follow-Up in GGT, SGOT, and SGPT Values of Alcoholic Men Who Abstained (N=63) or Resumed Drinking (N=19), Stage 2



DISCUSSION

These data indicate that percent increases in GGT, SGOT, and SGPT values over discharge values were significantly greater for alcoholic men who were drinking at follow-up than for subjects who remained abstinent. Drinkers were likely to show percent increases in GGT of ≥20%, in SGOT of ≥40%, or in SGPT of ≥20%, while abstainers typically had values at follow-up that were unchanged or lower than at discharge. Although use of a larger data set will eventually refine these cutoff percent changes, an increase in any of these three laboratory measures above an individual's value after 4 weeks of abstinence appears indicative of a return to drinking. This result holds true even though the rise is rather small and the test value remains within the clinical laboratory's so-called normal range. For example, to use data obtained directly from the alcoholic subjects in this study, an increase in GGT from 30 U/liter at discharge to 38 U/liter at follow-up (>20% increase) or in SGOT from 15 Karmen U/ml to 23 Karmen U/ml (>50% increase) is a relatively small change within our hospital's normal range. Nonetheless, both examples demonstrate increases that reliably indicated a return to active drinking in a previously abstinent alcoholic man.

This combination of percent increases was highly sensitive, since it identified more than 95% of the drinkers; at the same time, it was moderately specific in labeling more than 80% of the abstainers. The accuracy of this rule when it is applied to blood test values was established against outcome determined by multiple indicators, including review of legal and medical records and a series of interviews with the patient and at least one resource person.

The blood tests reported here are routinely available and use automated methods found in most clinical laboratories at minimal cost. Other automated instruments may provide different absolute enzyme values, but determinations of percent change are not likely to be affected.

In this study, assay methodologic error due to variable or prolonged periods of storage of serum, even with refrigeration, was minimized by running all samples on the day of the blood drawing and on the same automated instruments. Using these methods, our clinical laboratory has found that the intraindividual coefficients of variation are less than 2% for each of the three variables (GGT, SGOT, and SGPT) in healthy control subjects. Other investigators have reported that interassay variation ranges from 7.3% to 24.2% for SGOT (15, 16) and is less than 4% (16) for GGT; each of these percentages is considerably lower than the respective cutoff percentage used in our decision rule.

The rule itself involves only the simple calculation of percent change between prospectively measured blood values. The application of multiple test values in parallel combination (i.e., increases in GGT, SGOT, *or* SGPT) enhances the sensitive identification of active drinking, albeit with a loss of specificity when compared with using either single test values or serial combinations (i.e., GGT *and* SGOT) (14). In contrast to this approach involving the individual subject as his own control, dichotomous decisions about "normal" or "abnormal" blood values rely on large changes in laboratory values and are not sensitive indicators of early, more subtle changes in the patient. Other investigators have suggested that the simultaneous evaluation of multiple laboratory test results and their interrelationships, even within the "normal" range, can identify heavy drinkers (17). However, these procedures, which primarily use either linear or quadratic discriminant function analyses to differentiate alcoholics or heavy drinkers from healthy control subjects, require a relatively large number of tests for overall accuracy in classification. When one reduces the number of laboratory parameters from 35 to seven, the accuracy of the classification is considerably lessened (18). Further, the quadratic discriminant approach is viewed as a research technique that is not readily available for routine implementation in the clinical setting (17).

While the overall accuracy of classification is satisfactory, there may be other groups of alcoholic patients for whom application of our decision rule might be more or less useful. For example, in men with severe alcoholic liver disease such as cirrhosis, further consumption of alcohol may not result in increases in GGT or SGOT values (19). Also, in the present work, active drinkers at follow-up were defined as those men who consumed alcohol during the previous 14 days. While alcohol consumption was correlated with percent increases in GGT, SGOT, and SGPT values, we do not yet know the sensitivity of this rule in distinguishing sporadic drinkers from subjects abstinent for as long as 4 weeks. A third problem occurs with intake of some drugs, such as barbiturates or cough medications, and/or other factors, including duration of alcoholism, sex, age, obesity, and cigarette smoking, which could also affect GGT levels (12, 20) and influence the accuracy of the decision rule. We hope this paper will stimulate others to apply this approach to more diverse populations to further explore the heterogeneity of the change in enzyme values in drinkers and to establish the applicability of our decision rule in the general clinical setting.

Despite these limitations, application of this decision rule is likely to help in the early recognition of an alcoholic who has resumed drinking after treatment. Use of the clinical laboratory to measure changes in GGT, SGOT, and SGPT test values is an inexpensive and objective approach that could help clinicians detect recent alcohol use and, thus, institute treatment before drinking and associated problems escalate.

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The Psychiatrist as Legal Guardian

Robert M. Wettstein, M.D., and Loren H. Roth, M.D., M.P.H.

Most discussions about legal guardianship pertain to special populations, such as the mentally retarded or demented. Except for the case of refusal of antipsychotic medication, little has been written about using guardianship to authorize nonemergency treatment for a person who is mentally ill and treatable. The authors present several cases in which a consulting or administrative psychiatrist served as a temporary guardian for a hospitalized patient's personal affairs. The psychiatrist-guardian authorized diagnostic procedures or ECT for the temporarily incompetent patient and was then discharged as guardian. The authors discuss the problems and limitations of such a role for the psychiatrist.

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In some communities, legal guardianship is commonly used for persons with severely impaired capacities to provide for their own personal or financial needs. Guardianship may be appointed over the person's estate (when the respondent is unable to manage financial affairs), over the person (when the respondent is unable to manage personal affairs), or, often, over both.

Most discussions about legal guardianship pertain to special populations, such as the mentally retarded or demented. In recent years, use of a legal guardian for a person has become more common in jurisdictions in which involuntarily hospitalized psychiatric patients are permitted to refuse psychoactive medication. In these cases, to involuntarily administer medication to the patient hospital staff must petition a court to declare the patient incompetent to refuse medication. Either the appointed guardian or the court then decides whether the patient should receive the medication (1).

The use of legal guardianship in any context is frequently limited, however, by the unavailability of a person who is willing and able to act as legal guardian. Some states and counties fund a public guardian office, which is responsible for providing such individuals or services. In many locations, however, such a resource is lacking. Further, with the fear of liability, many potential guardians refuse to assume the necessary emotional, administrative, or legal responsibility for another individual. Thus, family members often refuse to act as even temporary guardians for a patient or may be unable to make surrogate decisions for the patient even if they have been appointed guardian because of interpersonal or intrapsychic conflict (2, 3). In addition, private guardianship over a person's financial affairs is often restricted by statute or practice to persons with sizable estates.

Consent for some forms of medical or psychiatric treatment usually may not be obtained from a power of attorney, although this has been proposed (4). In principle, power of attorney ceases when a person is no longer functionally or legally competent to initiate it. A durable power of attorney survives patient incompetency but still does not allow the granting of consent for medical treatment in many cases.

Now nearly forgotten is the earlier era when the superintendent of a state mental hospital acted as the de facto guardian for a patient who required medical or surgical procedures but could not consent to them and had no available relatives to consent. Developments in mental health law, particularly concerns about the superintendent's conflict of interest and the need for due process in guardianship proceedings, have eclipsed this traditional role for physician-administrators. The lessons of this earlier era are, however, still relevant.

Confronted with the unavailability of potential temporary guardians for several patients who appeared incompetent to consent to, or refuse, necessary treatment, a university-based psychiatric hospital began to use selected staff psychiatrists as guardians. This paper presents several of these cases, and some of the advantages and potential problems with such an arrangement are discussed. The paper will not review the many clinical and forensic issues involved in the definition and determination of whether a patient is incompetent to consent to treatment (5–7).

CASE REPORTS

Case 1 (no surrogate available): incompetent refusal of diagnostic procedures. Ms. A, a 67-year-old widow who lived alone, was committed for treatment of atypical psycho-

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sis. When a breast mass and middle lobe chest lesion were identified, she was transferred to a medical facility. Ms. A, however, refused breast biopsy and bronchoscopy, although she consented to a head CAT scan, chest CAT scan, bone scan, and mammogram, all of which revealed the possibility of metastatic breast cancer. She was returned to the psychiatric hospital for treatment of her psychosis.

Ms. A's mental status examination was remarkable for agitation, tangentiality, distractibility, suspiciousness, and loosely organized paranoid delusions about her medical care. Ms. A feared that her water and her food were poisoned and she believed that she was being harassed by outside individuals.

Ms. A refused the bronchoscopy and breast biopsy despite repeated attempts to assure her of their safety. She could not provide a reason for refusal except to indicate that she was "afraid." At times she agreed with the need for the tests but still refused them. Treatment with antipsychotic medication had little effect.

Because of the absence of relatives, a senior psychiatrist who held an administrative position in the hospital petitioned the court to be appointed temporary guardian of the person to authorize the diagnostic procedures. At her own request, Ms. A did not attend the guardianship hearing, and she did not have an attorney represent her. The psychiatrist, represented by the hospital's attorney, was appointed temporary guardian of the person.

Subsequent testing, authorized by the psychiatrist on Ms. A's behalf, revealed a breast carcinoma. After additional psychiatric treatment Ms. A's psychotic symptoms remitted, it then appeared that she understood the nature of her disease and her need for treatment, and she became competent to consent to the treatment. Temporary guardianship was terminated, and the petition for permanent guardianship was withdrawn. The treatment plan for the carcinoma, involving chemotherapy and radiation therapy, was formulated with Ms. A and implemented with her consent.

Case 2 (no surrogate available): incompetent refusal of ECT. Ms. B, a 71-year-old widow, was transferred to a psychiatric hospital from a state hospital on an involuntary order for treatment of a recurrent depressive disorder. Twenty years previously she had had another episode of depression, which responded to ECT. Her sister had died in an accident 6 months before the current admission.

On examination Ms. B was oriented to place, distractible, depressed, and angry; she had suicidal ideation and feelings of hopelessness but no indication of dementia. She was negativistic in the hospital, cursed and screamed at the staff, and refused to eat or get out of bed. At times she did not communicate any choice about whether to have ECT or indicated that the physician should decide for her. At other times she refused ECT but would not discuss the rationale for this. Her depressive cognitions interfered with her ability to rationally manipulate information about ECT.

Ms. B's husband had died 15 years previously; they had never had children. She had one living brother but instructed the staff not to contact him. There was no other family member or friend available to serve as surrogate decision maker. The attorney for her deceased sister's estate refused to become involved in Ms. B's care.

A staff psychiatrist and administrator of the hospital was appointed Ms. B's temporary guardian of the person to authorize ECT. Ms. B did not want to appear at her hearing or be represented by counsel. The guardian carefully reviewed the anticipated risks, benefits, and alternatives with the treatment staff and then signed the consent form for treatment.

Ms. B received 12 ECT treatments. Although her affect and behavior had improved somewhat at their conclusion, she did not attribute this improvement to the treatments. She indicated that she had been afraid of the ECT and disliked the period of post-ECT confusion. Further ECT was terminated when the guardian concluded that Ms. B had regained her competency to decide about ECT and that the maximum benefit from the treatment had been achieved.

Case 3 (unwilling surrogate): incompetent consent to ECT. Ms. C, an 81-year-old widow, was voluntarily transferred from a personal care home to a psychiatric hospital. She had symptoms of a major depressive disorder with psychotic features. She had had numerous psychiatric hospitalizations for depressive episodes and one course of ECT 10 years before this admission. Until she retired she had been a ballet teacher and had owned a studio.

On examination Ms. C was alert and oriented but had profound psychomotor retardation. Her speech was minimal and inaudible, had long latencies, and showed thought blocking. She frequently stopped in the middle of a sentence without completing her thought. Cognitive testing could not be conducted because of her mutism. Because of the severity of her depression, her failure to eat and resultant weight of 69 lb, and her history of a previous response to ECT, it was decided to proceed with ECT. Repeated attempts to discuss the risks, benefits, and alternatives to ECT with Ms. C were fruitless because of her pseudodementia.

Ms. C's husband had died 10 years previously. A younger brother had died 16 years previously. Her 43-year-old son lived in the area but had little contact with her. He did not want to serve as guardian but did not oppose the appointment of one. He did not wish to meet with the proposed guardian. He indicated that his mother had never cared for him and that he was "tired" of her problems.

A consulting staff psychiatrist petitioned the court to be appointed temporary guardian to authorize ECT. Ms. C was not represented by counsel at the ex parte hearing. After the guardian was appointed, Ms. C was civilly committed to the hospital according to the usual procedure.

A course of five treatments, without complication, was remarkably effective in treating Ms. C's disorder. Afterward she indicated she was pleased that a guardian had been appointed to consent to ECT for her. She acknowledged that no one in her family had been willing and able to do so, stating that she and her son had a distant relationship.

Ms. C returned to her personal care home. She stated that she wanted the guardian to continue to serve in that capacity to help her move to a different home. The guardian informed her that this was not necessary, since she was now capable of arranging this, but he suggested subsequent telephone contact with her.

The temporary legal guardianship was terminated. A 2-month telephone follow-up revealed that Ms. C continued to be grateful for her hospital treatment.

Case 4 (surrogate conflict of interest): incompetent consent to ECT. Ms. D, a 64-year-old married woman, was involuntarily hospitalized, by means of police petition, for treatment of major depressive disorder with psychotic features. She lived with her second husband, who allegedly neglected and abused her; she was found wandering in the street in an emaciated state with bruises and a fractured arm.

On examination Ms. D was disheveled and cachectic and had multiple facial ecchymoses. She had loose associations and persecutory auditory hallucinations. She stated that she had died, and she refused to eat. Treatment with medication had no effect. Five years previously she had been successfully treated with ECT. She did not object to the use of ECT or other treatment, stating simply that she wanted to be left alone and was "too tired" to talk about such things. She was unable to recall and manipulate information about ECT.

Ms. D had two brothers and two sisters, who lived in distant states; her son was institutionalized. The hospital decided not to ask Ms. D's husband to serve as guardian because of the question of spouse abuse, although he signed a waiver permitting a staff member to be the guardian.

A staff psychiatrist, who was the administrative head of the hospital, petitioned the court to appoint him Ms. D's temporary guardian to authorize ECT. Both the treating psychiatrist and the proposed guardian testified at the hearing; Ms. D was not present or represented by counsel. At the hearing, the court questioned the proposed guardian about the patient's psychiatric disorder and her insurance coverage for the hospitalization; the physician explained that the hospital would assume responsibility for any expenses not covered by insurance.

The guardian informed Ms. D that he had been appointed legal guardian for her and that he had authorized ECT. She asked no questions about this and asked him to leave her alone.

There was dramatic clinical improvement after six ECT treatments. When the guardian then reviewed his role with Ms. D, she was grateful that someone had been "watching over" her and had provided ECT. She decided to move to a personal care home rather than return home to her husband. The hospital attorney withdrew the petition for permanent guardianship. Upon discharge from the hospital, Ms. D expressed regret that the guardian would no longer serve as such for her. The hospital subsequently received several letters from her siblings, who expressed appreciation for its efforts.

DISCUSSION

In each of these cases, a staff psychiatrist at a university-based hospital acted as temporary guardian of the person for an inpatient. The use of a psychiatrist as temporary guardian in these and other cases was initiated when no family member or close friend was available to serve as legal guardian and community or state resources did not provide for one. Neither the physician-guardian nor the psychiatric hospital was compensated for the guardian's services. Treatment proceeded in each case without adverse clinical or legal outcome. Many of the patients subsequently were grateful for this legal and clinical intervention, a phenomenon reported in many patients who have been civilly committed (8, 9).

The approach taken in these cases offers several advantages for patient care in short-term psychiatric hospitals. The hospital can provide psychiatric treatment that might otherwise be unavailable because of the absence of consent. The underutilization of ECT has been previously noted in the literature (10, 11) and can perhaps be partly accounted for by the unavailability of persons who can give consent. In one study (12), one-quarter of the hospitalized depressed psychiatric patients for whom ECT was recommended were judged incompetent to decide about treatment. The absence of appropriate treatment for severe recurrent depression results in unnecessary patient morbidity and mortality and wasteful medical care. Second, the use of mental health staff as guardians may expedite hospital care when locating distant relatives or friends is time-consuming and costly (13). Saving time is important in the case of patients with limited insurance coverage who are placed in private hospitals. Third, the use of staff as guardians, rather than distant family or friends, may minimize the bias against certain forms of medical or psychiatric treatment. Finally, the use of hospital counsel without charge to the patient permits guardianship in cases where it would otherwise be unavailable.

The unavailability of a family member to give surrogate consent to treatment is likely when the patient is elderly. Parents, spouses, and siblings may already have died; children often live in distant places. Even if a family member is available, the limited resources of many elderly persons make it difficult to afford private counsel for guardianship. This lack of family and emotional support often tempts the treatment team to select a "friend" or acquaintance of the patient to act as guardian, although the possibility that such a person is more interested in the patient's estate than medical welfare is ever present. Often, however, even friends are not available.

This approach to legal guardianship of patients with treatable psychiatric disorders also presents several problems. A problem for the nonfamily surrogate decision maker for a geriatric patient is the unavailability of a "value history" of the patient. McCullough noted that when a physician deals with a patient of diminished competence, the physician "should be guided by the patient's previous values and beliefs in determining appropriate diagnostic and treatment interventions . . . . [Family members] become an important source to help the physician construct the required value history" (14, p. 153). Such a "substituted judgment" decision is nearly impossible in many geriatric cases, especially those in which the patient has not previously received the form of treatment currently proposed and there are no advance directives with regard to future psychiatric care. Apart from the history of ECT use in the patients of this cohort, the psychiatrist-guardians did not have access to such value histories and instead used medical best interests as their standard in decision making. Because of their medical training and experience, such physician-guardians are at risk of improperly neglecting patients' values that conflict with medical biases. The psychiatrist-guardian might, for example, authorize ECT for a nonconsenting or refusing patient who would have refused such treatment had he been competent to do so (15). While in theory the psychiatrist-guardian acts as a layman in making substitute decisions for the patient, in practice such a role runs contrary to the physician's professional socialization, which favors treatment when it appears beneficial.

Some unique features of Pennsylvania law and practice presented several problems for the psychiatrist/proposed guardians in these cases. The statute states that in the absence of a patient's informed consent, ECT can only be administered after a court order (16). This contrasts with the statutes in some other jurisdictions, in which family members who are not legal guardians can authorize ECT for an incompetent patient (17, 18). In practice, however, a Pennsylvania court does not adjudicate whether the patient should receive ECT but merely appoints the guardian who then decides the appropriate treatment. Second, state law does not formally provide for limited guardianship (19). Rather, a guardian of the person or of the estate may be appointed. In each case, therefore, the psychiatrist-guardian was responsible for all personal decisions of the patient but not for financial ones. These personal decisions included such nonmedical matters as disposition or residence; the psychiatrist in one case was legally in the position of being able to prohibit a patient from returning to live with her husband. More common, however, was the threat that should a patient fail to respond to the psychiatric treatment, the psychiatrist-guardian would be appointed permanent guardian of the person, even after discharge from the hospital. This potentiality eliminated the use of psychiatrist-guardians for patients who needed guardians but whose psychiatric disorders were less likely to respond to ECT (e.g., those with significant dementia).

The third way in which Pennsylvania differs from other states is that while the psychiatrist-guardian may be authorized to consent to ECT for the patient, the guardian may not admit a patient to a psychiatric hospital. Thus, each patient who entered the hospital voluntarily was subsequently civilly committed after the guardian was appointed. Finally, in this state, contrary to the trend elsewhere, a person for whom a guardianship petition is presented is not guaranteed legal counsel and frequently does not attend the guardianship hearing, although notice to the respondent is required (19, 20). The judge then attempts to act as the patient advocate. While this procedure has its deficiencies, including blurring of the parties' roles and conflicts between their interests, some may argue that it is particularly subject to abuse when the petitioner is a physician or mental health professional, since the patient may have even less opportunity to present contrary psychiatric evidence. Similarly, the petitioning physician-guardian may, perhaps inadvertently, use a less stringent test of competency to consent to treatment in order to coerce a marginally competent patient to have a medical treatment.

The psychiatrist-guardians in these cases were faced with other potential problems. The proposed guardian did not usually attend or testify at the guardianship hearing. In one case where the proposed psychiatrist-guardian did testify, however, the court essentially approached him as if he were the treating psychiatrist. Such an approach further compromises the psychiatrist-guardian's attempt to act as a layman rather than a physician. The patient, too, many confuse the psychiatrist-guardian with the treating psychiatrist. Second, in that case, the psychiatrist-guardian was a hospital administrator. Authorizing an extended course of treatment may conflict with such a guardian's administrative concerns about uncompensated hospital care. Any of these factors may influence the physician's willingness to act on behalf of the patient when the physician has reservations about the use or scope of his coercive authority.

Perhaps the most troublesome conflicts involve cases in which the available family members refuse to accept guardianship or ECT for their functionally incompetent relative, but the staff firmly believe such is indicated. In a case not presented here, the family members opposed even a petition for a staff member to serve as guardian of the person for the patient because it could have resulted in judicial review of the family's control of the patient's sizable estate. This refusal was not challenged, in part because it appeared unlikely that the patient would respond to ECT. Other cases in which the family irrationally opposes an appropriate course of ECT or other treatment are clearly foreseeable. In a derivative sense, psychiatrists (with occasional exceptions, such as child psychiatrists) do not formally act as patient advocates, although this has been recommended in the case of the elderly (4, 20, 21). Psychiatrists commonly, however, act as unofficial guardians of patients by opposing improper requests by families to hospitalize patients or administer other inappropriate treatments. Sparr and Roth (22) have argued that the clinician is "unavoidably the guardian of last resort for the patient"; the psychiatrist thus has an obligation to present the need for treatment to a court even though it may be opposed by the family. Psychiatrist-guardians clearly risk psychological and legal assault from family members in such cases. The need to work closely with the families of patients with diminished competence cannot be overstated.

There are other situations in which this approach may be of limited or no use. The psychiatrist-guardians in the cases presented here restricted their treatment authorizations to accepted medical diagnostic procedures or standard, time-limited psychiatric treatment. Further, in the case of ECT, authorized treatment usually restores the patient's competence to make decisions. It is doubtful whether a treating or consulting physician is suitable as a guardian in a medical setting in which chronic treatment or its withdrawal is at issue or where the guardian would have to assume permanent responsibility for all of the patient's affairs. This includes situations in which the proposed treatment is life sustaining, is experimental, or presents unusual risks to the patient. The interests of both patients and society in these cases may be better served by other mechanisms for surrogate decision making.

Finally, any mechanism that provides for medical treatment in the absence of informed consent by the patient is subject to abuse. Clinicians in all settings need to be alert to the possibility of excesses of authority. It is clearly advisable for the psychiatrist-guardian to be acting in consensus with members of the treating staff, the patient's family, and, to the maximal extent possible, the patient. The guardian should explain his role to the patient and attempt to involve the patient in decisions about treatment to the extent possible. The use of second opinions and consultations with other psychiatrists or attorneys is probably indispensable to the success of such a program.

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Psychiatry and the Criminal Justice System: Testing the Myths

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Several states are changing legislation and treatment programs for mentally ill offenders without knowing how current laws and programs operate. To address this problem the authors linked data from police records, court reports, and clinical files for 2,735 psychiatric referrals from the criminal justice system of Alaska from 1977 through 1981. They found that only 0.2%–2.0% of all schizophrenic persons in the community were arrested for violent crimes each year, accounting for 1.1%–2.3% of all arrests for violent crimes; that psychiatrists agreed about competency and responsibility in 79% of the cases evaluated by more than one clinician; and that a successful insanity defense occurred in 0.1% or less of all criminal cases.
(Am J Psychiatry 1988; 145:605–610)

Forensic psychiatry is a field that is long on controversy but short on data. National coverage of extraordinary cases such as the Hinckley trial (1) and highly publicized debates about the use of the insanity defense (2–4) have created a number of myths about forensic psychiatry and mentally ill offenders. The public perception is that schizophrenic patients frequently become violent and that involvement of psychiatrists in criminal cases often leads to "a battle of experts" that makes it easy for criminals to avoid conviction. These unsubstantiated beliefs are so pervasive that they have motivated several states to change legislation and treatment programs for mentally ill offenders (5–7). Changes include restrictions on use of the insanity defense and treatment of some mentally ill offenders in prisons instead of in hospitals. These changes are having a major impact on the practice of forensic psychiatry and on the management of mentally ill offenders.

To test popular beliefs about mentally ill offenders, a clear description of the actual practice of forensic psychiatry is needed. We therefore undertook a 5-year retrospective study in Alaska that integrated judicial, criminal, and psychiatric information on 2,735 forensic referrals. The study generated a large, unique data set that allowed us to examine the incidence, characteristics, and outcome of virtually all forensic referrals in the state.

METHOD

The study period was from the beginning of 1977 to the end of 1981. To be included in the study a person had to be 1) facing a criminal charge or in custody as a result of a criminal charge and 2) referred by the courts, lawyers, jails, or probation officers for psychiatric or psychological evaluation or treatment. Clinical files were located at the Alaska Psychiatric Institute (the only psychiatric hospital operating in Alaska from 1977 to 1981), community mental health clinics, and private clinics. Clinicians in the state who are knowledgeable about the forensic referral process estimated that this study captured 95% of all referrals made in the state. Court case numbers from the clinical files were sent to the Alaska court system, and court outcomes for 1,874 (88%) of 2,130 unduplicated criminal cases were obtained. Social Security numbers were sent to the Public Safety Department, and criminal histories were obtained for 1,671 (92%) of 1,816 individual patients.

Coding of the clinical data was done by 13 university students, and coding of the court and criminal history data was done by three university students. Both groups received 2 weeks' training. All coding was supervised closely and personally checked by the prin-

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cipal investigator (M.R.P.). A 120-item data sheet that included demographic, clinical, criminal, and legal items was completed for each referral. Psychiatric diagnoses from 1977 to 1979 used the old standards of APA (*DSM-II*), which are not completely compatible with the current standard diagnoses (*DSM-III*). This problem was resolved by using the 14 aggregated groups of diagnoses recommended by the National Institute of Mental Health (NIMH) (8) as the best method for making *DSM-II* to *DSM-III* comparisons. Offenses were classified according to the Alaska Crime Code (9), which divides offenses by severity and by type (i.e., against persons, against property, or other types). In 724 (34%) of the 2,130 unduplicated criminal cases the individual was charged with multiple crimes; only the most serious charge was considered in this analysis.

The three sources of information were collated and coded for each referral. In the 508 patients who had multiple referrals over the study period (28% of 1,816 individuals), demographic and historical data were cross-checked for consistency and any discrepancies were corrected. All identifying information was then removed (to ensure confidentiality), and the remaining data were analyzed. Population, criminal, and psychiatric data were obtained from state and national publications (10–17) and from data provided by local clinicians.

RESULTS

To emphasize the different perspectives for analyzing forensic services, we used three different units of analysis: the individual, the criminal case, and the referral. The study included 1,816 individuals. Some individuals were arrested more than once during the study period (range=1–12 referred arrests). A total of 2,130 unduplicated criminal cases were referred. Since some criminal cases were referred more than once (range=1–7 referrals per criminal case), there was a total of 2,735 referrals. Of these referrals, 2,226 (81%) were for mental health evaluation and 509 (19%) were for treatment.

Of the 1,816 individual patients, 1,569 (86.4%) were males, 198 (10.9%) were juveniles (i.e., under 18 years of age), 1,075 (59.2%) had never married, 804 (44.3%) were unemployed, and 766 (42.2%) had less than 12 years of education. Their mean±SD age was 28±10 years (range=11–78 years). Nonwhites (mostly Eskimos and other Native Americans) were overrepresented, accounting for 44% (N=726) of the 1,665 forensic patients for whom race was ascertained but only 23% (N=91,208) of the 400,035 general Alaskan population (χ^2=649.9, df=1, p<0.001).

The diagnostic breakdown of the 1,816 individual patients was as follows: 383 (21.1%) had alcohol-related disorders, 300 (16.5%) had schizophrenia, 276 (15.2%) had personality disorders, 231 (12.7%) had adjustment disorders, 120 (6.6%) had affective disorders, 388 (21.4%) had other (less frequent) mental disorders, and 118 (6.5%) had no mental disorder. Seven hundred twenty-six (40%) of the 1,816 patients had a history of psychiatric treatment before their first forensic referral.

Of the 1,671 patients for whom criminal histories were obtained, 1,053 (63%) had arrests or convictions before their first referral. For these 1,053 patients, the mean time from the most recent previous arrest to the index arrest (i.e., first referred arrest) was 29 months. Previous alcohol abuse, as reported by the clinician or as evidenced by previous conviction for alcohol-related crimes, was present in 890 (49%) of the 1,816 patients, and previous drug abuse was present in 508 (28%).

Type of Crime and Conviction Rates

Serious criminal cases were more likely to get referred. Violent crimes against persons (i.e., all types of assault and robbery) accounted for only 12% (N=10,271) of all arrests in the state for which the type of crime was specified (N=82,832), but they accounted for 43% (N=894) of the 2,090 referred criminal cases for which the type of crime was specified (χ^2=1782.2, df=1, p<0.001). Crimes against property (e.g., burglary, theft, trespass) accounted for 36% (N=747) of the 2,090 referred criminal cases, and "other crimes" (e.g., disorderly conduct and alcohol or drug offenses) accounted for 21% (N=449). The most common specific crimes were third-degree assault (N=227), which occurs if the victim is in fear of imminent physical injury; disorderly conduct (N=150); first-degree assault (N=119), which occurs if the defendant causes physical injury by means of a dangerous instrument; and first-degree sexual assault (N=117), which occurs if there is sexual penetration without consent. Of the 193 persons arrested for murder in Alaska over the 5 years of the study, 65 (34%) were referred for mental health evaluation.

Table 1 shows that patients with schizophrenia were not the most violent subgroup. Only 28% of the arrests of referred schizophrenic patients were for violent crimes, compared with 51% of the arrests of referred patients with alcohol-related disorders (χ^2=44.4, df=1, p<0.001) and 52% of the arrests of referred patients with personality disorders (χ^2=41.1, df=1, p<0.001). Schizophrenic patients accounted for 13% (N=118) of all referred violent crimes (N=894) and, given the assumption that all schizophrenic patients arrested for violent crimes were referred, 1.1% (N=118) of all arrests for violent crimes (N=10,292).

The overall conviction rate for referred criminal cases in which the legal outcome was ascertained was 57%; 759 (72%) of the 1,046 convicted subjects were given jail terms (mean length of sentence=32 months; median=2 months). Table 1 shows that conviction rates varied both by type of crime and by diagnosis. For each type of crime, schizophrenic patients were significantly less likely to be convicted than other

TABLE 1. Diagnoses, Types of Crimes, and Legal Outcomes in Criminal Cases Referred for Psychiatric Evaluation in Alaska, 1977–1981

Type of Crime and Legal Outcome	Alcohol-Related Disorders (N=428)	Schizophrenia (N=420)	Personality Disorders (N=314)	All Other Diagnoses[a] (N=928)	Total[b] (N=2,090)
Violent crime					
Number of cases	217	118	162	397	894
Number of cases for which verdict was known	206	110	149	349	814
Number of guilty verdicts	142	34	107	233	516
Percent of guilty verdicts[c]	69	31	72	67	63
Crime against property					
Number of cases	121	203	104	319	747
Number of cases for which verdict was known	111	195	99	239	644
Number of guilty verdicts	81	57	74	150	362
Percent of guilty verdicts[c]	73	29	75	63	56
Other type of crime					
Number of cases	90	99	48	212	449
Number of cases for which verdict was known	83	99	44	162	388
Number of guilty verdicts	46	16	24	82	168
Percent of guilty verdicts[c]	55	16	55	51	43
Total					
Number of cases	428	420	314	928	2,090
Number of cases for which verdict was known	400	404	292	750	1,846
Number of guilty verdicts	269	107	205	465	1,046
Percent of guilt verdicts[c]	67	26	70	62	57

[a] Includes 121 criminal cases for which the diagnosis was "no mental disorder."

[b] The total does not include 40 referred criminal cases for which the type of crime was not specified.

[c] Percents based on number of cases for which verdict was known.

TABLE 2. Clinical Findings in Criminal Cases Evaluated by Clinicians for Competency to Stand Trial or Responsibility at the Time of the Crime in Alaska, 1977–1981

	Competency Evaluated (N=1,063)					Responsibility Evaluated (N=951)				
				Guilty Verdicts[a]					Guilty Verdicts[a]	
Clinical Finding	N	%	Verdict Known	N	%	N	%	Verdict Known	N	%
Cases evaluated by one clinician	981	92.3	907	524	57.8	885	93.1	817	478	58.5
Patient found not competent or not responsible	90	8.5	87	12	13.8	126	13.2	118	32	27.1
Patient found competent or responsible	891	83.8	821	502	61.1	759	79.8	699	446	63.8
Cases evaluated by more than one clinician	82[b]	7.7	75	52	69.3	66[c]	6.9	63	45	71.4
Clinicians agreed	67	6.3	63	44	69.8	50	5.3	48	34	70.8
Patient found not competent or not responsible	4	0.4	4	0	0.0	8	0.8	8	2	25.0
Patient found competent or responsible	63	5.9	59	44	74.6	42	4.4	40	32	80.0
Clinicians disagreed	15	1.4	12	8	66.7	16	1.7	15	11	73.3
Total	1,063	100.0	982	576	58.7	951	100.0	880	523	59.4

[a] Percents based on number of cases for which verdict was known.

[b] In one case four clinicians disagreed about competence, in two cases three clinicians disagreed, in four cases three clinicians agreed the patient was competent, and in one case three clinicians agreed the patient was not competent. All other cases were evaluated by two clinicians.

[c] In three cases three clinicians disagreed about responsibility, and in two cases three clinicians agreed the patient was responsible. All other cases were evaluated by two clinicians.

diagnostic groups of patients (all 2×2 chi-squares> 27.2; all df=1; all p values<0.001).

Outcomes in Criminal Cases Evaluated for Competency and Responsibility

Half (N=1,063) of the 2,130 criminal cases were evaluated for competency to stand trial, and 45% (N=951) were evaluated for mental responsibility at the time of the alleged offense by using the American Law Institute test (18). In 109 (10%) of the 1,063 criminal cases evaluated for competency, the patient was considered not competent by at least one clinician; 65 (60%) of these 109 patients had a diagnosis of schizophrenia. In 150 (16%) of the 951 criminal cases evaluated for responsibility, the patient was considered not responsible by at least one clinician; 81 (54%) of these 150 patients had a diagnosis of schizophrenia.

Table 2 shows that clinicians' evaluations of defendants' competence and responsibility were significantly associated with the verdicts received. Patients considered not competent by one or more clinicians were less likely to be found guilty than patients considered competent ($\chi^2=68.7$, df=1, p<0.001). Patients considered not responsible were less likely to be found guilty than patients considered responsible ($\chi^2=51.4$, df=1, $p<0.001$). However, 45 (32%) of the 141 patients considered not responsible by one or more clinicians were subsequently convicted.

Only a small proportion of cases were evaluated for competency or responsibility by more than one clinician, and in these cases clinical agreement was the norm. Of the 82 cases evaluated for competency by more than one clinician, clinicians disagreed in 15 cases (18%). In 11 of these 15 cases there was a corresponding disagreement about diagnosis. Of the 66 cases evaluated for responsibility by more than one clinician, clinicians disagreed in 16 cases (24%). In nine of these 16 cases the clinicians also disagreed about the patient's diagnosis. Most patients evaluated by more than one clinician were considered either responsible or competent, and thus the high agreement of clinicians was partly due to chance. Moreover, clinicians' determinations were not always independent—a second evaluator may have read the previous evaluator's report. The kappas for the concordance (19) of competency and responsibility determinations were, respectively, 0.32 and 0.45. The courts found defendants guilty in 19 (70%) of the 27 cases in which clinicians disagreed about competency or responsibility.

Court "battles" between clinicians were rare. In only seven criminal cases, all of which involved violent crimes, did two or more clinicians make court appearances. Clinicians agreed on diagnosis in all seven cases but disagreed on competency in two cases and on responsibility in one case. Of the six cases in which the verdict was ascertained, five (83%) resulted in conviction.

Not guilty by reason of insanity findings by the court were uncommon. In 150 criminal cases at least one clinician considered the patient not responsible at the time of the crime: 29 (19%) of these defendants were found not guilty by reason of insanity, 67 (45%) had the charges dropped, 45 (30%) were found guilty, and for nine (6%) the legal outcome was unknown. Generally, in the more serious cases the defendants were found not guilty by reason of insanity, and the less serious cases were dropped—20 of the 29 findings of not guilty by reason of insanity involved violent crimes, but only 13 of the 67 dropped cases involved violent crimes ($\chi^2=19.9$, df=1, $p<0.001$). The yearly incidence of 14.4 findings of not guilty by reason of insanity per million population compares to the 1976–1978 yearly incidence of 3 per million in New York State and 30 per million in Oregon (20).

The maximum possible number of defendants acquitted or cases dismissed as a result of a clinician's judgment of not responsible was 105 (29 plus 67 plus 9). This represents only 11% of the 951 cases evaluated for responsibility, 4.9% of all 2,130 referred criminal cases, and 0.1% of all 95,229 criminal cases in Alaska. In two-thirds of these 105 cases the patient had a primary diagnosis of schizophrenia.

DISCUSSION

This study has several limitations. In adopting a "systems" approach it combined all types of forensic referrals; it thus obscured many of the important differences between different subgroups of forensic patients. Clinicians' reports to the court were usually quite detailed, and so, with the exception of the specifics about substance abuse, the quality of the clinical data was good, but it was not possible to verify clinical findings by any external standard. The quality of the court outcome and criminal history data was dependent on the thoroughness and accuracy of the computerized files from which most of this information was obtained. Cross-checks between the three sources of data suggested that the reliability of these data sets was good, but there was no external test of reliability. Failure to obtain 5% of the referrals, 12% of the court outcomes, and 8% of the criminal histories may have introduced unrecognized biases.

Atypical characteristics of Alaska that could affect the interpretation of these findings are the high level of alcohol abuse and the large numbers of Eskimos and other Native Americans in the nonwhite population. Alaska has the third highest per capita sale of alcohol of the 50 states (21) and the 20th highest rate of alcohol-related crimes (22). The proportion of forensic patients with alcohol-related disorders in Alaska may therefore be higher than it is elsewhere. Nonwhites are arrested at significantly higher rates than whites throughout the United States (23, 24); it is therefore not surprising that this study found a disproportionate number of nonwhites among referred arrestees. (The characteristics of Native American mentally ill offenders have been described in an earlier paper [25].)

Given these caveats, this study provides an empirical overview of forensic psychiatry in Alaska from 1977 to 1981 that refutes certain misconceptions about forensic psychiatry and mentally ill offenders. But how generalizable are results from Alaska? On the one hand, the methods of managing mentally ill offenders are in such a state of flux throughout the United States that any specific findings are necessarily time-limited and jurisdiction-limited. On the other hand, the problems faced in trying to manage mentally ill offenders are similar across jurisdictions, and so the methods developed to identify and analyze such problems in Alaska should prove useful elsewhere.

Testing the Myths

Dangerousness of schizophrenic patients. This study provides new data on the controversy about the dangerousness of schizophrenic patients. Since the practice of diverting violent schizophrenic offenders to the mental health system rather than to the courts was not common in Alaska at the time of the study and since violent schizophrenic patients are very likely to get psychiatric referral when they appear in criminal court, it is safe to assume that from 50% to 100% of the schizophrenic patients arrested for violent crimes were referred for psychiatric evaluation. There were 118 referrals of schizophrenic persons charged with violent crimes during the 5-year study period. If these 118 referrals represent a 50% referral rate, there were from 24 (118 divided by 5) to 47 (236 divided by 5) arrests of schizophrenic persons for violent crimes each year. If the period prevalence of schizophrenia in Alaska is similar to the estimated period prevalence in the United States—from 6 per 1,000 to 30 per 1,000 (26)—0.2% (24 of 12,056) to 2.0% (47 of 2,411) of the schizophrenic persons in Alaska were arrested for violent crimes each year. The lower estimate of 0.2% assumes a 100% referral rate and a prevalence of 30 per 1,000; the higher estimate of 2.0% assumes a 50% referral rate and a prevalence of 6 per 1,000. We believe that the lower estimate of period prevalence (6 per 1,000) and the higher estimate of referral rate (100%) are most accurate, so our best estimate is that 1.0% (24 of 2,411) of the schizophrenic persons in Alaska are arrested for violent crimes each year. The corresponding rate for Alaskans without schizophrenia is 0.5% (2,034 of 399,440). (These figures are not adjusted for duplicate arrests of the same person in 1 year.)

Some schizophrenic patients are violent, but the unfortunate stereotype of schizophrenic persons as violent and dangerous is not supported by epidemiological studies of crime (27), by studies of prison populations (28), or by observational data on encounters between police and citizens (29). Moreover, if we assume a 50% to 100% rate of referral from criminal courts, schizophrenic patients account for only 1.1%–2.3% (118 of 10,292 to 236 of 10,292) of all arrests for violent crimes. Thus, schizophrenic patients are not to any appreciable extent responsible for the high level of violence in our society.

Conflicting psychiatric testimony. Judges and juries are rarely faced with the dilemma of expert psychiatric witnesses who have differing opinions. The vast majority of forensic cases are unambiguous or do not merit the expense of multiple evaluations, and so only one psychiatric opinion is requested. In Alaska, 8% of the criminal cases evaluated for competency and 7% of the criminal cases evaluated for responsibility were evaluated by more than one clinician. The rate of multiple-clinician referral might be higher in states with more forensic psychiatrists available, but multiple referrals are clearly not the norm and probably account for only a small proportion of forensic cases.

Even in the doubtful cases where more than one psychiatrist was involved and the adversarial system would be expected to increase disagreement, clinicians agreed about relevant legal questions in 79% of the cases. Similarly high interexaminer agreement has been found in most studies of agreement among forensic psychiatrists (30). This high interrater agreement may be partly because of chance and partly because clinicians' determinations are not independent. But in the real-world practice of forensic psychiatry the point of view of the judge and jury is most important: in Alaska, contradictory psychiatric opinions were presented to the court in 1.5% of all psychiatrically evaluated criminal cases (0.03% of all criminal cases); in 70% of these disputed cases the defendant was found guilty. The highly publicized court battles of experts are rare; when they do occur, they are unlikely to result in exculpation.

The insanity defense. A "successful" insanity defense, i.e., leading either to a not guilty by reason of insanity finding or to a dismissal of charges, accounted for (at most) 0.1% of all criminal cases in Alaska. Estimates from other jurisdictions are consistently below 1% (31). Changes in the insanity defense or limitation of psychiatric testimony may prevent a few flagrant abuses, but it is not likely to make a substantial improvement in the protection of the public. Preoccupation with the insanity defense has deflected public and professional attention from more important problems in the management of mentally ill offenders.

CONCLUSIONS

Evaluation of the *actual* operation of forensic laws and programs needs to be more comprehensive and more systematic. Legislators, jurists, and mental health administrators need a realistic overview before they can rationally devise and implement policies for the management of mentally ill offenders. Moreover, it will be impossible to determine the relative costs of the current legislative and programmatic changes and the degree to which these changes achieve their stated goals until ongoing cross-institutional data collection is implemented. This study demonstrates the feasibility of such a data collection system that links information on forensic patients across institutions while maintaining individual confidentiality. Until such information systems are developed, we will remain vulnerable to the cycle of dramatic actions and reactions that occurs whenever there is public outcry about a criminal case involving a mentally ill offender.

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Privatization: Economic Opportunity and Public Health

One aspect of the "remedicalization" of psychiatry is the provision of psychiatric care within the mainstream of medical economics. The broad movement toward the privatization of health care is now a "megatrend" in mental health economics, as Dorwart and Schlesinger describe in this issue of the *Journal.* Privatization of psychiatric care is a mixed blessing, however, as the authors point out.

The enhancement of economic opportunity through a deregulated competitive market in the delivery of health care has led to a phenomenal growth and diversification in the private provision of acute and chronic health services. The "let all flowers bloom" approach of the market has only been matched by the increased complexity of the regulations of federal, state, and local governments. The numbers of institutional and professional providers have increased, as has the large and differentiated group of third-party payers, both public and private. Costs of care continue to escalate, and there is evidence that large numbers of consumers are unable to pay many of their medical bills (1).

Psychiatric care, although largely a government enterprise for over a hundred years, has witnessed a large growth in private hospital beds, especially in the proprietary sector. Investor-owned health care companies have perceived a distinct economic opportunity, and in states with fewer regulatory constraints, they have increased the number of psychiatric beds at an accelerating rate. Perhaps in response to this, some psychiatric insurance coverage has been decreasing, and the U.S. business community is beginning to take a close look at their expenditures for acute and longer term mental health care (2). The unfortunate backlash could lead to a decreasing ability of the middle class to afford timely psychiatric care (3); access to psychiatric care by the poor and near poor may become more acute in the years to come.

It is clear that for psychiatric care the market is a poor mechanism for efficient and fair rationing of scarce dollars. There is a need for strong government regulation and financing in order to deal effectively with needed treatment and support for the acutely and chronically mentally ill, many of whom today are homeless and in the streets and have no access to general health and mental health care. Psychiatric leadership is crucial if we are to carefully manage our resources to provide the most effective treatment to those patients who are most in need. Mindless privatization of health care will create a legacy of disenchantment with mainstream financing of psychiatric care and with the capacity for psychiatry to be the medical specialty qualified to diagnose and treat mental disorders. As Dorwart and Schlesinger suggest, we should carefully monitor the current trends with good research and data collection and be proactive in the public and private sectors in order to ensure the quality as well as the efficiency of the treatment enterprise.

Although there are proponents for a radical restructuring of medical care, either in the direction of a publicly financed and controlled national health system or in the direction of a totally deregulated competitive system, it is likely that we will continue to have a mixed public and private system for the foreseeable future. With our federal system, we have at least 50 experiments in the delivery of public and private psychiatric care and in the provision of acute and chronic treatment services. We need to find the correct mix of private and public financing, as well as public and private service delivery, in order to ensure access and quality within the inevitable economic constraints. As clinician-leaders, psychiatrists must play an active role in this public and private policy debate, since its outcome will determine future professional practice and the availability of treatment.

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Tardive Dyskinesia in Bipolar Affective Disorder: Aging, Cognitive Dysfunction, Course of Illness, and Exposure to Neuroleptics and Lithium

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Cognitive function, course of illness, and medication history were assessed in 42 bipolar patients evaluated for the presence of involuntary movements. Among the 25 patients 55 years old or older, the 16 with involuntary movements were not distinguished from the nine without involuntary movements by past or current exposure to neuroleptics, anticholinergics, or carbamazepine, but they showed poorer cognitive function, had fewer major depressive episodes, and had received briefer exposure to lithium. The association between involuntary movements and cognitive dysfunction parallels that found in schizophrenia, suggesting that similar neurological processes may contribute to vulnerability to involuntary movements in the major functional psychoses.

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An increasing body of evidence suggests that schizophrenic patients with involuntary movements (tardive dyskinesia) are particularly likely to show cognitive dysfunction and/or negative symptoms in comparison with patients who have had indistinguishable exposure to neuroleptics but fail to show such movements (1–6). On review of the available studies (7), it appears that such associations are less consistently found in younger patients but are particularly reliable in older, chronically ill populations. Since cognitive dysfunction and negative symptoms are those features of chronic schizophrenic illness which have been most consistently associated with structural brain abnormalities in CAT scan and nuclear magnetic resonance (NMR) imaging studies (8–11), vulnerability to the emergence of involuntary movements may bear some relation to such cerebral pathology (4, 6, 7).

Epidemiological studies have established that involuntary movements can emerge in patients with disorders other than schizophrenia who have received long-term neuroleptic treatment (12). Indeed, it has been suggested (13, 14) that patients with affective disorders may be particularly vulnerable to the emergence of involuntary movements. If associations between involuntary movements and specific features of the clinical state in schizophrenia are a clue to a more general determinant of predisposition to movement disorders, it would be necessary to demonstrate similar associations in nonschizophrenic disorders, particularly in affective illness. In the present study, we assessed involuntary movements and cognitive function in patients with bipolar affective disorder in relation to the extent of their exposure to neuroleptics and to lithium.

METHOD

The subjects of this study were 42 patients who were either living in St. Davnet's Hospital or attending an outpatient clinic in its community care service. All subjects satisfied *DSM-III* criteria for a diagnosis of bipolar affective disorder. They were between 23 and 82 years of age and consented to assessment. All 42 patients had been treated with neuroleptics, and 33 of the patients had also received lithium. The assessment procedures were the same as those applied in our previous studies of schizophrenic patients and have been described elsewhere (4, 6).

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TABLE 1. Characteristics and Medication History of Bipolar Patients With (N=16) or Without (N=9) Involuntary Movements

	Patients With Involuntary Movements		Patients Without Involuntary Movements	
Item	Mean	SD	Mean	SD
Characteristics				
Age (years)	64.3	8.8	63.9	6.3
Duration of illness (years)	27.4	6.8	26.6	11.7
Number of major affective episodes	13.5	4.0	18.3	6.0
Manic	7.1	2.8	7.2	3.6
Depressive[a]	6.4	3.2	11.1	5.1
Cognitive function score[b]	6.9	1.6	8.9	1.2
Medication history				
Duration of lithium treatment (years)[c]	6.4	3.5	10.1	2.4
Neuroleptic treatment				
Age at first treatment (years)	42.9	10.4	43.9	7.8
Duration of treatment (years)	15.3	7.2	13.3	9.9
Mean dose (mg/day of chlorpromazine equivalents)	335.0	120.0	244.0	84.0
Current dose (mg/day of chlorpromazine equivalents)[d]	164.0	90.0	364.0	357.0
Duration of anticholinergic treatment (years)[e]	5.6	3.7	3.4	3.1
Duration of carbamazepine treatment (years)[f]	1.9	2.4	1.8	0.5

[a] Significant difference between groups (Mann-Whitney U=27, $p<0.05$ with Bonferroni adjustment).

[b] Significant difference between groups (Mann-Whitney U=25.5, $p<0.05$ with Bonferroni adjustment).

[c] Significant difference between groups (Mann-Whitney U=8, $p<0.05$ with Bonferroni adjustment). Twelve (75%) of the patients with and seven (78%) of the patients without involuntary movements had received lithium in the past. Four (25%) of those with and six (67%) of those without involuntary movements were currently receiving lithium.

[d] Eleven (69%) of the patients with and seven (78%) of the patients without involuntary movements were currently receiving neuroleptics.

[e] Fourteen (88%) of the patients with and eight (89%) of the patients without involuntary movements had received anticholinergics in the past; two (13%) of those with and two (22%) of those without involuntary movements were currently receiving anticholinergics.

[f] Six (38%) of the patients with and three (33%) of the patients without involuntary movements had received carbamazepine in the past; four (25%) of those with and none of those without involuntary movements were currently receiving carbamazepine.

Movement disorders were evaluated with the Abnormal Involuntary Movement Scale (AIMS) (15). As previously noted in schizophrenia (16), involuntary movements of the limbs and trunk were rare. These may represent a pathophysiologically distinct subsyndrome (17, 18). In all further discussion, therefore, references to involuntary movements relate to classical buccal-lingual-masticatory dyskinesia, defined by the presence of at least mild but definitely abnormal movements of one or more orofacial areas (6). For further comparison with our previous studies in schizophrenia (6), cognitive function was assessed by using a previously described 10-question mental test that evaluated the basic functions of orientation, awareness, and immediate memory (4).

Only after assessments had been completed were demographic details, clinical information, and medication histories obtained from subsequent review of case notes. The pattern of the manic and depressive episodes detailed in the patients' clinical records was documented longitudinally from their first presentations. These episodes were documented so that we could count the number of affective episodes experienced by each patient. Changes in mood that were of sufficient prominence to be recorded by the patients' consultant psychiatrists as a major episode or relapse constituted affective episodes. All such judgments preceded the present study and were made independently of it.

As we have described in detail elsewhere (19), several facets of hospital life in rural Ireland have contributed to an unusually detailed data base of decades of drug treatment. For determination of the neuroleptic treatment measures specified in table 1, doses were converted to chlorpromazine equivalents by using standard tables (20). The total duration of exposure and the presence or absence of current exposure to anticholinergics, lithium, and carbamazepine were also determined. Data are expressed as means± SD or as percentage prevalences and were analyzed by using the Mann-Whitney U test or the Fisher exact probability test (two-tailed).

RESULTS

The overall prevalence of involuntary movements was 40% (17 of 42 patients); they were evident in 10 of 25 male patients and seven of 17 female patients. The prevalence of involuntary movements was 0% in patients younger than 35 years (none of four patients), 8% in those 36–54 years old (one of 13 patients), and 64% in those 55 years old or older (16 of 25 patients). Because of the rarity of involuntary movements in patients younger than 55, all subsequent data comparisons relate to the 25 patients 55 years old or older.

Nine of these 25 patients (four men and five women) did not have involuntary movements; 16 (10 men and six women) did. The mean orofacial AIMS score of the 16 patients with involuntary movements was 4.3±1.5 (range=2–7). Eleven (69%) of the patients with and five (56%) of those without involuntary movements were currently inpatients. Inpatients and outpatients were equally represented among those with and without involuntary movements.

As shown in table 1, the patients with and without involuntary movements could not be distinguished from each other by the variables of age, duration of illness, age at which neuroleptics were first prescribed, duration of neuroleptic therapy, mean daily dose of neuroleptics over that total duration of exposure, or current daily dose of neuroleptics. They were also not distinguished by duration of exposure to anticholinergics (to which most patients had been exposed) or carbamazepine (which had been used occasionally) or by current treatment with such agents.

Clinical variables, however, readily distinguished patients in whom involuntary movements were present or absent. As shown in table 1, patients with involuntary movements had lower cognitive function scores. They had also experienced fewer depressive but not fewer manic episodes and had received less prolonged exposure to lithium.

On the day of evaluation for movement disorder, 12 patients with involuntary movements were euthymic, one was depressed, and three were hypomanic; seven of the patients without involuntary movements were euthymic, one was depressed, and one had a mixed affective state.

DISCUSSION

The prevalence of involuntary movements in patients with bipolar affective disorder increased markedly with age. This confirms the findings of previous studies conducted in a variety of heterogeneous populations and in homogeneous schizophrenic groups (12, 21). For this reason, associations between each of the remaining study variables and the presence of involuntary movements were examined in the patients 55 years old and older. Patients with and without involuntary movements could not be distinguished either by general demographic characteristics or by typical indexes of previous and current exposure to neuroleptics. Most patients had also received anticholinergics, and a smaller number had received carbamazepine; neither the duration of previous exposure to nor current treatment with either medication distinguished patients with and without involuntary movements.

A relationship between cumulative duration of neuroleptic treatment and the presence of involuntary movements in bipolar outpatients has been described by Mukherjee et al. (14). However, the mean age of the largely inpatient population in our analysis was more than 20 years greater than that of the outpatients in the study of Mukherjee et al., and the mean duration of neuroleptic treatment in our patients was almost double. These fundamental differences make it difficult to compare the two studies directly. In our present study, patients without involuntary movements tended to receive higher current daily doses of neuroleptics, perhaps suggesting some masking effect or reflecting differing requirements for treatment. However, current neuroleptic exposure was highly variable and did not differ significantly between the two groups.

Clinical features of their bipolar illnesses readily distinguished patients with and without movement disorders, however. Patients with involuntary movements showed considerably poorer cognitive function. Such an association has been found in several studies in schizophrenic groups, especially those involving older, chronically ill patients (1–7), and a preliminary report (22) found that patients with affective disorder who had involuntary movements showed some impairments on cognitive testing. In schizophrenia, cognitive deterioration has been widely (but not invariably) associated with CAT scan and NMR imaging evidence of structural brain pathology (8–11). Similar cognitive and structural changes, most commonly lateral ventricular enlargement, have been demonstrated in patients with affective disorder, especially those with chronic bipolar disorder (9, 10, 23, 24). Although such neurological processes may be more evident in chronically ill schizophrenic patients with involuntary movements than in those without such movements (7, 25, 26), any similar association has yet to be investigated directly in affective disorder.

Bipolar patients with involuntary movements were also found to have had fewer depressive but not fewer manic episodes than those without involuntary movements. Although there have been reports of state-dependent dyskinesia (27, 28), the great majority of our patients were euthymic at motor assessment. Thus, our data can neither be explained in such terms nor can they contribute to the debate on this issue. In one study (14), the number of hospitalizations for manic episodes did not independently distinguish younger bipolar outpatients with and without involuntary movements. Prospective studies would be required to establish the reliability and any clinical or biological significance of the present finding.

The association between the presence of involuntary movements and reduced exposure to lithium replicates a 1986 report (14) and also presents great difficulties of interpretation. Our cross-sectional and retrospective analysis would be consistent with but does not prove an action of lithium to protect against the emergence (or otherwise reduce the expression) of dyskinesia (14). However, the fact that patients with involuntary movements had had less exposure to lithium might be related in some way to the fact that they experienced fewer depressive episodes. Clearly, since both the number of manic relapses and the duration of exposure to neuroleptics failed to show similar associations, any such relationship would have to be complex, and prospective studies would again seem necessary to clarify the point. Although we do not exclude the possibility that aspects of the putative neurochemical strata of affective disorder may contribute to vulnerability to involuntary movements (14, 27, 28), we have no data relating to this issue.

The present data, which suggest an association between predisposition to involuntary movements and cognitive deterioration in bipolar affective disorder, are similar to findings in schizophrenia (1–7). There has been renewed interest in the older concept of "unitary psychosis" (29). One interpretation of our findings would be that similar neurological processes may contribute to vulnerability to the emergence of involuntary movements across the traditional boundaries between the major functional psychoses.

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Hypothalamic Pathology in the Neuroleptic Malignant Syndrome

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The pathogenesis of the neuroleptic malignant syndrome is currently unclear, and no specific morphological abnormalities in the CNS of victims of neuroleptic malignant syndrome have been described. The authors report a case of neuroleptic malignant syndrome with recent foci of necrosis in the anterior and lateral hypothalamic nuclei. They discuss the role of tricyclic antidepressants, monoamine oxidase inhibitors, and neuroleptics in the development of this syndrome. They conclude that although the pathogenesis of the neuroleptic malignant syndrome is still not clear, necrosis of the hypothalamic nuclei may be pathognomonic for this syndrome.

(Am J Psychiatry 1988; 145:617–620)

The neuroleptic malignant syndrome was first described by Delay and Deniker (1) in the 1960s. Although its incidence is rare, it has been reported more frequently in the last few years. This may be due to increased alertness on the part of physicians as well as to the increase in the use of neuroleptic medications.

The pathogenesis of this condition remains unclear. It has been compared to malignant hyperthermia (2), a rare but often fatal complication of general anesthesia, although certain features of both conditions are distinctive. The neuroleptic malignant syndrome appears to be a complication of chemotherapy with dopamine receptor blocking agents involving increased muscular activity and a hypothesized hypothalamic disturbance that would impair heat dissipation (3, 4). There are also suggestions that neuroleptic treatment would result in a disturbance in the hypothalamic-adrenal axis associated with excessive catecholamine secretion (5).

To our knowledge, this is the first report of pathological abnormalities in the nervous system of a victim of neuroleptic malignant syndrome.

CASE REPORT

Ms. A, a 48-year-old white woman, was referred for treatment of a depression that had proven refractory to treatment for the previous 3 years. She had been in active treatment in an acute general hospital for 6 months before transfer for continuing treatment. She had failed to respond to a variety of tricyclic antidepressants in adequate doses as well as to ECT. Her depressive syndrome had waxed and waned in severity for the previous 20 years, leading to a number of suicide attempts.

Ms. A had a family history of affective disorder in a sister and a paternal aunt. Her father was alcoholic, as was her husband.

At the time of her admission, Ms. A was experiencing overt vegetative and core symptoms of depression, particularly suicidal ideation. She was diagnosed as having a major depressive episode with recurrent unipolar depressive disorder and was allowed a 7-day drug-free washout period on entrance to the hospital to assess her condition. The drugs she had been taking were clomipramine, 25 mg b.i.d., and flurazepam, 15 mg h.s. During the drug-free period, a physical examination was completed; results were within normal limits. Results of laboratory investigations, including EEG, CBC, urine analysis, electrolytes, blood urea nitrogen, creatinine, uric acid, phosphate, albumin and proteins, cholesterol, bilirubin, liver enzymes, and cardiac enzymes were all within normal limits.

Ms. A's fasting glucose level was elevated to 195 mg/100 ml. A 5-hour glucose tolerance test showed a serum glucose level of 211 mg/100 ml 60 minutes after glucose loading, but her glucose level was within normal limits 2 hours after glucose loading and thereafter. Immunoglobulin assays showed that IGM and IGTG levels were within normal limits and the IGA level was slightly below normal (80 mg/dl). The dexamethasone suppression test (DST) was also done. Ms. A's pre-dexamethasone-administration serum cortisol was 17.2 µg/dl, and she suppressed her production of cortisol to 1.1 µg/dl at 4:00 p.m. the day following the administration of 1 mg of dexamethasone. Results of chest X-ray, EEG, and thyroid function tests were within normal limits

It should be noted that Ms. A's past medical history showed no substantial medical problems except a tendency toward low blood pressure. She had had an appendectomy 30 years earlier, hiatal hernia repair 8 years earlier, and a hysterectomy 4 years before this admission.

Seven days after admission she was started on a zimelidine drug study program, but her depression—particularly her suicidal ideation—continued to worsen, so she was withdrawn from the zimelidine study after having received active medication for 1 week. Over the next 14 days she received a

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series of six ECTs, along with 150 mg of imipramine h.s. A full organic workup was repeated following the discontinuation of zimelidine and before starting the ECT. As in the initial workup, all test results were essentially within normal limits. Because her depression continued to worsen, a second series of seven ECTs was started over the next 19 days. The dose of imipramine was increased to 200 mg h.s. Ms. A's imipramine blood level at that time was 401 ng/ml (total tricyclic). In spite of ECT and imipramine treatment, she remained depressed.

ECT was stopped after the second series of ECTs, and a regimen combining the tricyclic drug (imipramine) and a monoamine oxidase inhibitor (MAOI) (phenelzine, 15 mg every morning) was started. On subsequent days, due to the worsening of depression, phenelzine was titrated slowly upward until the patient was receiving 60 mg/day. Sixteen days after she started this regimen, she showed signs of increasing impulsiveness, agitation, and anxiety. Her suicidal ideation again was becoming stronger and she attempted to hang herself in the hospital. At this point, the dose of phenelzine was raised to 75 mg/day and, in response to the appearance and then an increase of mood-congruent delusions, oral perphenazine, 4 mg q.i.d., was started and raised to 8 mg q.i.d. 48 hours later. Other than flurazepam, 30 mg h.s. as needed, no other medication was prescribed.

Five days later the patient was found to be drowsy when seen on morning rounds. She was able to respond to questions and was oriented, however. At noon that same day, she was found to be diaphoretic and had a rectal temperature of 41.1°C; her blood pressure was 150/100 mm Hg, her pulse was 140/minute, and her respiration rate was 32/minute. Laboratory tests done at that point showed a slight elevation in both the WBC count and serum transaminase and a moderate increase in the creatinine phosphokinase level.

On neurological examination, the patient was found to show extrapyramidal symptoms, including tremors of the hands and lips, rigidity of the arms and wrists, and clenched jaw. At this point she was diagnosed as having neuroleptic malignant syndrome (6), but because of the acuteness and severity of her distress, she was transferred to the intensive care unit of a nearby general hospital, where it was thought that she could be better managed. She died 24 hours later.

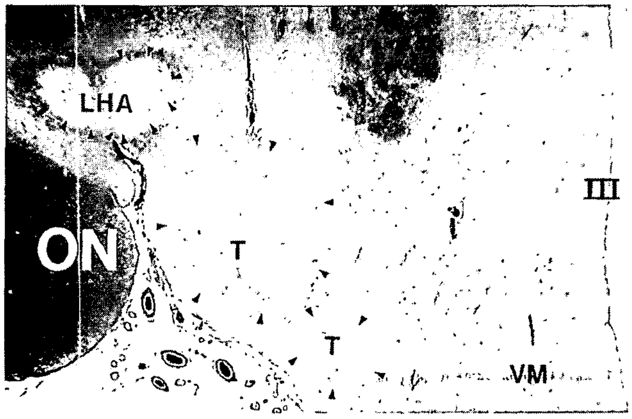
Neither bromocriptine nor dantrolene was used at either center in attempting to treat this patient. The following follow-up laboratory results were recorded: WBC remained slightly elevated, and creatine phosphokinase rose slightly to 401 U/liter (normal=10–120 U/liter).

The possibility that Ms. A's neuroleptic malignant syndrome was caused by an overdose of imipramine and phenelzine or by an interaction between the tricyclic imipramine and the MAOI phenelzine was considered. These possibilities were not supported by toxicology testing.

POST-MORTEM EXAMINATION

The autopsy was performed 4 hours after death. The only important pathological finding was generalized congestion of visceral organs and meninges. Microscopic examination of visceral organs showed no evidence of disseminated intravascular thrombosis or infection. Neuropathological examination was performed after 2 weeks of fixation of the brain in formalin. The brain weighed approximately 1500 g. There was no evidence of abnormalities on external inspection and in coronal sections of the cerebrum, cerebellum, brainstem, and spinal cord. The standard set of sections from representative areas of the brain and spinal cord and an entire hypothalamic area between the olfactory trigone and pulvinar were removed for paraffin embedding and microscopic examination. The blocks of hypothalamus were cut at several levels approximately 2 mm apart. The sections of the brain were stained with one or all of the following methods: hematoxylin and eosin, Luxol fast blue plus cresyl violet plus eosin, and Luxol fast blue with periodic acid Schiff reaction.

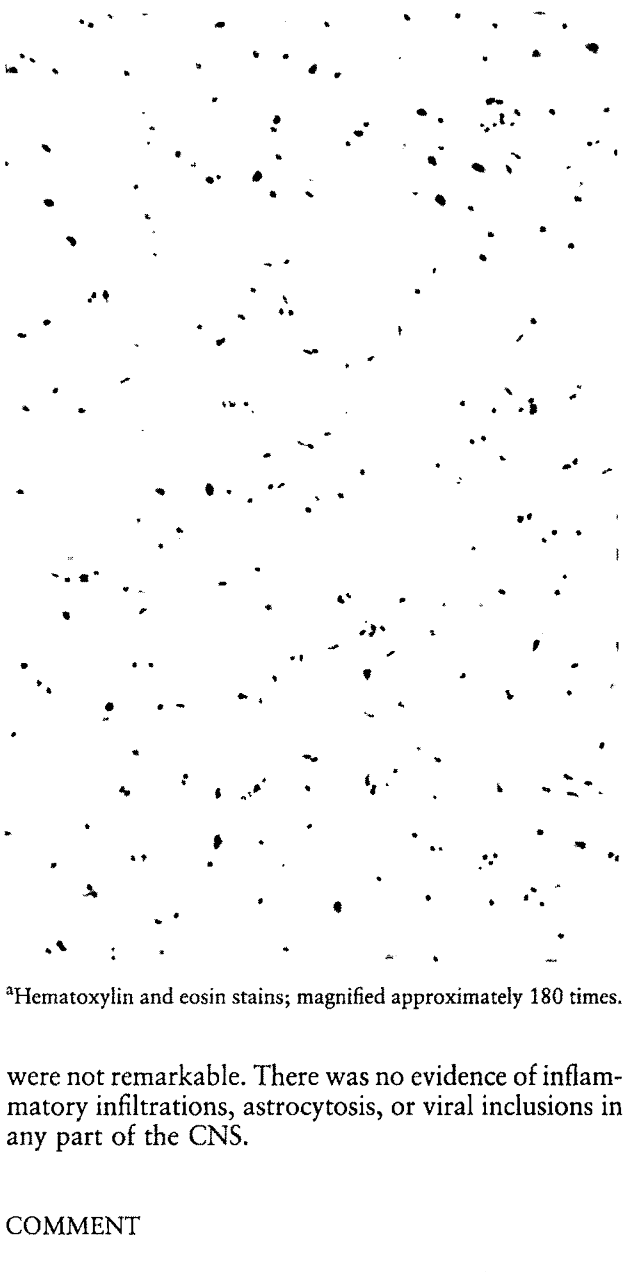
FIGURE 1. Circumscribed Foci of an Early Necrosis in the Hypothalamus of a Patient Who Died of Neuroleptic Malignant Syndrome[a]



[a] ON=optic nerve, LHA=lateral hypothalamic area, T=tuberal nuclei (probably lateral and medial tuberal nucleus) (7, 8), III=third ventricle. Hematoxylin and eosin stain; magnified approximately 12 times. Arrows indicate necrosis.

Microscopic examination of multiple sections of the hypothalamus revealed conspicuous bilateral foci of pyknosis and disintegration of neurons and sponginess of the neuropil in the anterior hypothalamus (figures 1 and 2). These changes were slightly asymmetrical and limited to the group of neurons in the lateral hypothalamic area and tuberal nuclei. Also, a few pyknotic neurons were present in the ventral-medial hypothalamic nucleus. All the remaining hypothalamic nuclei showed perfect morphological preservation. Very few scattered petechial hemorrhages were present indiscriminately in the periventricular gray matter of the anterior and posterior hypothalamus. The cerebral cortex revealed widespread small foci of nuclear pyknosis with increased cytoplasmic acidophilia, vacuolation, and disintegration of neurons. These changes were slightly more prominent in the third cortical layers, in the Sommer's sectors of Ammon's horn and generally in the depths of sulci. The white matter displayed scattered small areas of poorly demarcated paleness of myelin. Purkinje cells of the cerebellum as well as many neurons in the pons showed cytoplasmic acidophilia and shrinkage of the nuclei. The basal ganglia, thalami, medulla oblongata, and spinal cord

FIGURE 2. Pyknosis, Disintegration, and Loss of Neurons in the Lateral Tuberal Nucleus of a Patient Who Died of Neuroleptic Malignant Syndrome[a]



[a]Hematoxylin and eosin stains; magnified approximately 180 times.

were not remarkable. There was no evidence of inflammatory infiltrations, astrocytosis, or viral inclusions in any part of the CNS.

COMMENT

Neuroleptic malignant syndrome has been associated with both phenothiazine and nonphenothiazine antipsychotics. High-potency neuroleptics such as haloperidol and fluphenazine have been the most frequent offenders. Some case reports involving neuroleptic malignant syndrome showed that antipsychotics were used in combination with other medications. Although treatment with neuroleptics is usually considered the sine qua non in the pathogenesis of the neuroleptic malignant syndrome, it also has been reported in association with other drugs that do not have antipsychotic properties, such as dopamine-depleting drugs (9), and after discontinuation of a levodopa-carbidopa combination (10).

The pathogenesis of neuroleptic malignant syndrome is at present unclear. It is thought that altered thermal regulation in the syndrome is due to neuroleptic-induced dopamine receptor blockade in the basal ganglia, which raises the generation of heat through muscle contraction, and in the hypothalamus, which impairs heat dissipation. The complex process of regulation of internal temperature involves several sites in the spinal cord and brain. Of particular importance here is the presence of multifocal early necrosis in the preoptic anterior hypothalamus that is involved in the thermoregulation of normal health.

To the best of our knowledge, there was no evidence of substantial morphological abnormalities in the CNS in the previously reported fatal cases of neuroleptic malignant syndrome (3, 11). In general, the morphological changes in the CNS of our patient were similar in nature and distribution to those of anoxia-ischemia (12) and were most likely secondary to extreme elevation of body temperature. Previous post-mortem studies of patients who died of heat stroke demonstrated abnormalities indistinguishable from that of anoxic-ischemic changes (13, 14), possibly due to an increase of the cerebral metabolic rate and relative deficiency of oxygen during hyperthermia (15, 16). As in our patient, the brains from these patients displayed petechial hemorrhages distributed along the third and fourth ventricles and showed nonspecific loss and degeneration of neurons in the cerebral and cerebellar cortex or in the subcortical gray structures (14, 15, 1[illegible]). However, necrosis of the hypothalamic nuclei does not occur in uncomplicated anoxia-ischemia, and it has not been reported in simple hyperthermia or heat stroke alone (14, 15).

In view of the experimental evidence indicating the role of the anterior hypothalamic nuclei (1[illegible], 19)—particularly the preoptic medial nucleus (20)—in temperature regulation, the presence of early necrosis in this area in our patient may indicate the relevance of this lesion to the development of neuroleptic malignant syndrome. However, neither the lateral hypothalamic area nor tuberal nuclei are known to be directly involved in temperature regulation (21). Because of the close topographical and functional association of all the hypothalamic nuclei, one may expect that any lesion in this area will adversely affect more than a single regulatory mechanism. It has been established that monoamines (dopamine, norepinephrine, and serotonin) are produced by many hypothalamic neurons, including the tuberoinfundibular group. It is also known that monoamines may induce hyperthermia in monkeys (22). Therefore, it is possible that necrosis of any of these closely spaced neuronal groups or an injury to their axonal connections may lead to uninhibited release of neurotransmitters that indirectly affect the adjacent centers of temperature regulation. Obviously, on morphological grounds we cannot be certain whether tuberal and lateral hypothalamic lesions develop primarily as a result of pharmacological treatment or secondarily due to temperature elevation.

Absence of substantial abnormalities in other hypothalamic groups of neurons supports the observation of Fox et al. (19) that the occurrence of lesions in the anterior hypothalamic area is characteristic of the pathological conditions associated with abnormal body temperature.

In our patient the possibility of a somewhat unique etiopathic situation also might have existed in which the role of both the tricyclic antidepressant and the MAOI, along with the neuroleptic, might have facilitated the development of neuroleptic malignant syndrome. This possibility has also been suggested by other authors (23). For instance, the monoamines norepinephrine and serotonin in the hypothalamus are directly involved in temperature regulation. The temperature responses to direct application of monoamines into the hypothalamus vary depending on the species used. They are unknown in man, but in the monkey (as already noted), serotonin induces hyperthermia (22). Drug-induced changes in the action of these monoamines could therefore explain reported cases of hyperthermia following overdoses with MAOIs alone (24) or in combination with tricyclic antidepressants (25). Administration of MAOIs has been shown to be associated with an increase in hypothalamic serotonin and norepinephrine concentrations (26). Tricyclic antidepressants, in addition to blocking monoamine uptake presynaptically, are also known to produce an inhibition of postsynaptic adrenergic receptor function when present in higher concentrations (27). These effects, in combination with dopamine receptor blockade produced by perphenazine, could have contributed to dysregulation of hypothalamic temperature-controlling mechanisms.

Inhibition of diaphoresis by peripheral anticholinergic effects of neuroleptics has also been thought to contribute to the development of malignant syndromes involving psychoactive medication. When depression of thermal regulation in the hypothalamus is superimposed on an already physically exhausted and compromised individual, the likelihood of hyperthermia becomes more probable.

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Subtle and Underrecognized Side Effects of Neuroleptic Treatment in Children With Tourette's Disorder

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A variety of side effects developed in children treated with neuroleptics for Tourette's disorder. Of 208 children, 34 manifested dose-related symptoms of dysphoria, nine experienced a worsening of symptoms of Tourette's disorder that was attributed to akathisia, five became hostile and aggressive, three developed "fog states" that disappeared with discontinuation of neuroleptics or treatment with primidone, and three experienced symptoms of tardive dyskinesia that resolved with time. This data base of neuroleptic-treated children with Tourette's disorder demonstrates a variety of subtle and underrecognized side effects that may not be as readily discernible in children receiving neuroleptics for a primary psychiatric disorder.

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It is generally agreed that Gilles de la Tourette's disorder is an acceptable indication for the use of neuroleptic medication with children. If the symptoms are severe, neuroleptic treatment may be indicated on a continuous basis for many years, even for life. Although most patients with Tourette's disorder can be maintained successfully on a regimen of small doses of medications, side effects are a major consideration in their use. Since these children are not, as a rule, psychotic, acutely disturbed, or retarded, they are often active participants in their own care. They desire treatment and appreciate the benefits of medication, but they and their parents are extremely alert to the presence of side effects. Some investigators feel that they are more prone and alert to side effects than other patients (1, 2).

During the past 17 years I have treated 208 patients with Tourette's disorder under the age of 18 years who have been taking neuroleptic medication for some period of time. Some of these children were referred to me because of complications due to neuroleptic treatment. The most common neuroleptic used was haloperidol, but some patients with side effects were switched from haloperidol to pimozide, fluphenazine, or other closely related neuroleptics. In order to evaluate the nature of side effects experienced by this group of patients, a retrospective review of the cases was undertaken. No attempt was made to compare the effects of one neuroleptic to another.

FINDINGS

Commonly recognized side effects such as sedation, dystonic reactions, parkinsonism, and cardiovascular changes were surprisingly uncommon in all patients, probably because medication was given in small doses and the dose was increased slowly in most cases. However, some patients exhibited more unusual adverse reactions which were not as readily recognizable as such.

Thirty-four children developed symptoms of dysphoria or depression that were dose related and appeared even with conservative dose levels. In every case a "threshold dose" could be identified above which the patient would complain of dysphoria and below which dysphoric symptoms were absent. Threshold doses varied from 1 to 6.5 mg/day of haloperidol and from 5 to 18 mg/day of pimozide. One child had dysphoric symptoms while taking 5 mg/day of fluphenazine. Typical symptoms included crying spells, irritability, social withdrawal, anxiety, fearfulness, and preoccupation with morbid subject matter. Younger children became whiny and clinging. Adolescents became moody and expressed suicidal thoughts. Two adolescents and one 11-year-old child required tricyclic antidepressants. School phobias appeared in eight children (ages 5–14 years). In two of them school phobia was the most prominent symptom, but in all eight children there were depressive symptoms along with school phobia. The following is a typical case study.

Case 1. Dennis first developed symptoms of Tourette's disorder at age 7. The diagnosis was made 2 years later, at which time his symptoms included coprolalia and marked obsessive-compulsive behavior. After an unsuccessful trial with clonidine, Dennis was treated with haloperidol. At a dose level of 1 mg/day his tics were significantly diminished, although coprolalia and obsessive symptoms continued. The

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dose was raised gradually over the next 6 months to 5 mg/day. At that dose he quite suddenly became whiny, clinging, and tearful. Thoughts of death and mutilation predominated. He became very reluctant to attend school, where he had previously been quite comfortable. He expressed an urge to cut himself with scissors or put an electric wire in his mouth. Haloperidol was immediately lowered to 4 mg/day. An improvement in mood and behavior was noted about a week later and continued until 4 months later when his parents raised the dose of haloperidol again to 5 mg/day (coprolalia was a continued concern). Several days later all of the previous dysphoric signs and symptoms appeared again. With a subsequent decrease of haloperidol Dennis returned to his "normal self." He has subsequently done reasonably well with lower doses of medication. Coprolalia has been a consistent problem, but he has found ways to control it most of the time.

Nine children developed akathisia that seemed to "drive" the symptoms of Tourette's disorder. Typically, these children had an initial improvement with neuroleptic medication that was negated by a further increase in dose. Threshold doses ranged from 1 to 20 mg/day of haloperidol and 4 to 15 mg/day of pimozide. Above the threshold dose these patients' symptoms of Tourette's disorder (motor and phonic tics and even obsessive-compulsive behavior) worsened while they displayed clear signs or symptoms of akathisia. This sequence of responses to neuroleptic treatment can easily mislead the treating physician, who may increase medication again and again in an effort to control symptoms of Tourette's disorder. Akathisia may go unnoticed and restlessness may be attributed purely to Tourette's disorder, particularly in young children who cannot describe their inner sensations.

Case 2. Jason began to have tics at age 4. A diagnosis was made at the age of 7, but no treatment was required until age 10. At that time he was placed on a regimen of haloperidol by a neurologist. He experienced an initial improvement in tic symptoms, which was encouraging. The dose was gradually raised over the next few months, since it seemed to the physician and to Jason's parents that his symptoms of Tourette's disorder were gradually getting worse instead of better. He had been a good student before treatment, but he became unable to concentrate on his work. Because of increasingly loud and frequent vocalizations, restlessness, and irritability, he became a disruptive presence in his classroom. At home he could not sit still long enough even to eat meals or watch television. Nevertheless, he complained of being too tired to play sports with his friends. The dose of haloperidol was raised again and again, since his symptoms of Tourette's disorder were then quite severe. At a daily dose of 24 mg he was thought not only to have a marked exacerbation of Tourette's disorder but also to have a behavior problem. The latter was attributed to his feelings of helplessness regarding the symptoms of Tourette's disorder.

Jason's parents were dismayed and baffled by his personality change. They decided to bring him to me for a consultation. The dose of haloperidol was then gradually decreased to 2 mg/day. His "behavior problem" improved as the dose was reduced, and the symptoms of Tourette's disorder were simultaneously ameliorated. At a dose of 2 mg/day he felt quite well, but he and his parents elected to discontinue haloperidol. He has done well for the past 5 years with clonidine treatment. While the tics have not been quite so well controlled as they were with small doses of haloperidol, he has never had an exacerbation similar to the one that he experienced with larger doses.

Four adolescent boys and one 10-year-old boy became hostile and aggressive with haloperidol or pimozide treatment. The pattern was similar to those described previously in that there was a definite threshold dose above which aggressive behavior was noted and below which the children were "normal." The threshold dose for pimozide was 8 mg/day (see case 3) and it varied for haloperidol from 4 to 7 mg/day. All five patients became increasingly irritable and were subject to explosive and regressive behavior. The aggressivity was unusual for these boys and was experienced as ego-dystonic by them. Whether these outbursts of aggressive behavior were manifestations of akathisia is not entirely clear but is strongly suspected.

Case 3. Mark had had marked symptoms typical of Tourette's disorder since the age of 5. He had been treated rather successfully with haloperidol for several years until the age of 15, when an increase in medication was called for and it was found that cognitive blunting occurred above the level of 8 mg/day of haloperidol. It was hoped that Mark might do better with pimozide, which had just been released for use in the United States. However, when pimozide treatment was started and the dose was raised to 12 mg/day, Mark began to have explosive outbursts of temper unlike any he had had before. These outbursts occurred two to three times weekly, most frequently in the evenings, when, with the slightest provocation, he would start yelling, throwing things, pounding his fists, and even physically attacking his mother and brother. After these episodes he would appear to be filled with remorse and stated that he did not know why he had been so angry "at nothing." At first his parents attributed these temper tantrums to various stresses of adolescence. They resisted the suggestion that the dose of pimozide be lowered and stated that they would rather have their son "this way," lively and alert, than the way he had been during haloperidol treatment. However, life with Mark soon became quite unbearable, and the dose of pimozide was lowered to 10 mg/day, with considerable improvement. At 8 mg/day he was "his old self" but was still "more alive" than he had been during haloperidol treatment. His symptoms of Tourette's disorder changed little, if at all, with the decrease. Several months later Mark himself raised the dose of pimozide to 10 mg/day, but after only a few days he felt his temper again becoming explosive. He has been maintained on a regimen of 8 mg/day or less of pimozide for the past 2½ years. His symptoms have been only partially controlled, but he has felt well and has learned to cope with the tics he has.

Frank psychomotor seizures were experienced by two adolescent boys receiving low doses of haloperidol (1–3 mg/day). Both of these patients had abnormal EEGs with epileptiform features before the use of haloperidol, but neither had experienced any seizures. In addition to the frank seizures, one boy began experiencing "fog states." Two other adolescent boys receiving haloperidol also experienced fog states, although their EEGs had never been clearly abnormal (tracings were never obtained during a fog state). The fog states consisted of episodes during which the patients felt out of touch with, but not unaware of, their surroundings for minutes to hours at a time. Two of these patients responded to treatment with primidone and one to discontinuation of haloperidol. These fog states have been described by Shapiro et al. (1) only with high doses of haloperidol (more than 15 mg/day). Although the etiology of the fog states has been thought to be uncertain, it appears from my patients' response to primidone that they are indeed partial seizures. Case 4 gives a typical example of the fog state phenomenon.

Case 4. Larry began treatment for symptoms of Tourette's disorder at age 14. He did well initially with haloperidol treatment. However, after a few months, at a dose level of 3 mg/day, he began experiencing discrete episodes that began with an anxious feeling and proceeded within seconds to a fixation on asking himself certain questions over and over again. During these repetitive questioning thoughts he felt remote from his surroundings. He was able to answer simple questions put to him or to proceed with whatever he was doing, but only with great difficulty. He was aware of being in an unusual state of mind. Occasionally these fog states were accompanied by drooling and lip smacking; they lasted from a few minutes to as long as 3 hours and were sometimes precipitated by bright lights. Afterward he often felt tired and wanted to sleep. Several months later Larry had two clear-cut psychomotor seizures with total loss of contact with his surroundings. The fog states disappeared along with the frank seizures when he was treated with primidone in addition to haloperidol. Several years later he was able to discontinue both haloperidol and primidone without any recurrence of seizure activity or fog states.

Three patients developed abnormal movements, distinguishable from their Tourette's disorder movements, after treatment with haloperidol (dose range, 2–5 mg/day). Two of these patients had received haloperidol treatment for 5 and 3 years, respectively. One patient, age 17, developed choreic movements of the extremities as well as some choreic oral-buccal-lingual dyskinesia after taking haloperidol for 15 months. In all three cases the tardive dyskinesia resolved weeks to months after discontinuation of haloperidol. Withdrawal dyskinesias were not consistently recorded, although my impression is that they were more common than the dyskinesias occurring with a stable dose of neuroleptic.

DISCUSSION

From this group of children with Gilles de la Tourette's disorder it is apparent that there are a variety of subtle side effects of neuroleptic medication that are not well documented in the literature and may easily go unrecognized in clinical practice. The dysphoria described in this study is clearly an organic affective syndrome. Sometimes the symptoms are subtle and would not necessarily prompt a physician to think in terms of depression. However, if the neuroleptic is continued or the dose is increased, mild dysphoria may turn to frank depression. It is my impression that dysphoric symptoms account for a significant percentage of the cases of noncompliance with neuroleptic treatment. Nevertheless, *DSM-III-R*, while defining organic mood syndrome, does not suggest neuroleptic medication as an etiological factor.

School phobia has received attention over the past few years as a specific side effect of both haloperidol and pimozide treatment of Tourette's disorder (3, 4). It has been my experience, however, that this symptom does not exist alone but only as a manifestation of the dysphoric syndrome associated with these medications (5).

Akathisia, a common side effect of neuroleptic treatment, may be most distressing to patients and yet it is often unrecognized and its impact is underrated by physicians. This may be particularly true with respect to pediatric patients, in whom restlessness may so easily be obscured by hyperactive or stereotypic behaviors. It has been shown that akathisia may worsen psychosis and cause violent behavior as well as exacerbate the symptoms of Tourette's disorder (6–8). The aggressive behavior described here as secondary to neuroleptic treatment may in fact be a response to akathisic sensations that wax and wane. The danger when these reactions are misunderstood is that medication may be given in increasing doses, resulting in a vicious circle of escalating doses interacting with iatrogenic behavior problems.

Frank seizures are not often mistaken for other disease entities. However, fog states, as described in the present study, were a source of considerable confusion to several physicians. They were variously attributed to migraine, catatonia, hysteria, and malingering. They have yet to be documented by EEG, which would clarify their true nature. They have, however, been most definitely associated with haloperidol treatment, even in low doses.

There is still little known about the risk of tardive dyskinesia in children. This disorder has been reported most commonly in those children with preexisting neurologic dysfunctions (9). However, some investigators have found a surprisingly low prevalence of tardive dyskinesia in patients with Tourette's disorder (10). The diagnosis of tardive dyskinesia is complicated considerably by the preexistence of other abnormal movements attributable to Tourette's disorder. Since there is at least one report of persistent tardive dyskinesia after haloperidol treatment of Tourette's disorder, the condition should, however, be a matter of concern (11).

The particular patient population described in this article is perhaps atypical, even for Tourette's disorder. Many of these children were referred specifically because they were having difficulties with medication. Another problem with this study is that there was only one rater. The subtlety of some side effects increases the chances of bias. While overdiagnosis of certain reactions may have occurred, this has hopefully been balanced by the existence of other cases not reported because they were not so clearly dose related.

Whether some of the side effects discussed in this article are peculiar to patients with Tourette's disorder is not known. To my knowledge, there are no reports of school phobia or fog states in other populations as a result of haloperidol treatment. I believe that this is most likely due to the unique group that patients with Tourette's disorder comprise. Other children and adults receiving haloperidol are acutely agitated, psychotic, developmentally impaired, or retarded. The more subtle side effects of neuroleptics thus may be more apparent in children with Tourette's disorder, but it is important to ask if they exist with the same frequency in other children treated with neuroleptics.

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Alprazolam Dependence in Seven Patients

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The authors report on seven patients who met the DSM-III-R *criteria for psychoactive substance (alprazolam) dependence. All had withdrawal symptoms, six demonstrated tolerance, and at least four had substantial social or occupational impairment secondary to drug use. All seven patients had begun taking alprazolam as treatment for anxiety or depression. Six patients abused other drugs or alcohol, either in the past or concurrently. Doses of alprazolam ranged from 2 to 12 mg/day, and duration of use was 6 months to 3 years. The potential for dependence should be considered when prescribing alprazolam.*

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Dependence on benzodiazepines has been increasingly recognized (1–4). Alprazolam, a triazolobenzodiazepine, is absorbed rapidly (peak plasma concentration is reached within 1–2 hours) and is cleared more rapidly than many oxidized benzodiazepines (6–16 hours) (5)—factors that have been hypothesized as increasing the possibility of its inducing abuse or dependence (2, 4). Earlier onset and greater severity of withdrawal symptoms have been demonstrated with benzodiazepines that have shorter half-lives (4).

Withdrawal syndromes have been reported in patients who abruptly discontinue alprazolam after taking it in doses of 4–10 mg/day (6–9). Withdrawal symptoms range from agitation, tachypnea, palpitations, depersonalization, and perceptual distortion to delirium and seizures. Mellman and Uhde (10) documented a withdrawal syndrome with increased anxiety and increased plasma cortisol levels during gradual tapering of alprazolam.

We have been impressed by the increasing number of patients in our referral practice who take alprazolam and by the finding that a sizable minority appear to have problems with dependence, either on alprazolam alone or in combination with dependence on alcohol or other drugs. We report on seven cases that represent a spectrum of these patients and present case histories of three of them.

CASE REPORTS

Case 1. Ms. A, a 27-year-old single white woman who worked as a legal secretary, had been seen by a psychiatrist for complaints of anxiety and depression. She began taking alprazolam, 0.5 mg t.i.d. Over the following 3 years, the alprazolam was gradually increased to 8–10 mg/day, under her physician's supervision, because of her increasing anxiety. Attempts to taper the alprazolam led to complaints of headaches and tremors. Between doses of alprazolam, Ms. A would experience fleeting chest and abdominal pains, headaches, irritability, and anxiety, which would be relieved by her next dose of alprazolam. She noted increased irritability and subsequent difficulties with her co-workers; she did not go to work on several occasions because she felt "too hungover." Her family and local psychiatrist were concerned about her use of alprazolam, but she was unable to taper her use of the drug on her own.

Ms. A had had no previous formal psychiatric history. She had occasionally drunk one-half to one bottle of wine (once or twice a month) and had used amphetamines (up to one tablet daily) for 2 years when she was working at two jobs. She had subsequently quit her second job and discontinued use of amphetamines and alcohol (because of her concern about this use) a year before she began to take alprazolam. Two months before admission to the hospital she had begun to drink sherry, 60–90 ml/night.

She was admitted to her local hospital and alprazolam was withdrawn over 3 weeks. She then attended a 28-day inpatient alcohol and drug treatment program. There was no recurrent anxiety or depression during that period.

Case 2. Ms. B, a 38-year-old thrice-married white woman, was initially seen with her husband because of chronic marital discord. For the previous year, her local psychiatrist had prescribed imipramine, 200 mg/day, for complaints of anxiety and depression; in the previous 6 months, alprazolam, 0.5 mg t.i.d., had been added. She increased her use of alprazolam to approximately 2 mg q.i.d., against her physician's orders, and she supplemented her intake with her husband's alprazolam. She had between-dose and morning anxiety symptoms and a preoccupation with alprazolam. Ms. B's attempts to taper her intake of the drug were unsuccessful because of the increased anxiety that resulted, and her husband became concerned about her drug use.

On initial evaluation, Ms. B appeared to be intoxicated, with slurred speech; she did not have vegetative signs or symptoms of depression. She was admitted to our Alcoholism and Drug Dependence Unit, and the alprazolam was withdrawn by using chlordiazepoxide over 7 days; she had no major withdrawal symptoms. However, after 10 days, she became dissatisfied with group therapy and left against medical advice.

Ms. B had a long, complex medical and psychiatric

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history. Four abdominal and pelvic operations for pain complaints had not been successful in relieving her pain. She had been in a 3-week outpatient psychotherapy program several years earlier in an attempt to deal with her multiple somatic complaints and concern about her attractiveness and poorly defined ambitions. She was diagnosed as having conversion symptoms and a histrionic character style.

Her history included a suicide attempt because of difficulties in a relationship with a man when she was in her teens and a psychiatric hospitalization for a "nervous breakdown" with poorly defined symptoms after a divorce when she was in her early 20s.

Ms. B admitted that she had drunk up to 150 ml/day of liquor 10–15 years earlier but stated that because of her concern and her family's concern about her alcohol use, she had limited herself to one glass of wine on major holidays since then.

Case 3. Dr. C, a 31-year-old married white physician, was referred for chemical dependency evaluation. Three years previously he had had a major depression with vegetative signs and symptoms and anxious features. The depressive symptoms responded to amoxapine, 100 mg/day, and chlordiazepoxide, 25 mg t.i.d. These were discontinued after 3 months.

One year previously he had had a recurrence of depression with vegetative signs and symptoms. He had placed himself on a regimen of amoxapine, up to 150 mg/day, and alprazolam, 1 mg t.i.d. The depressive symptoms abated. Three months later he began to see a psychiatrist, who continued the alprazolam but changed the antidepressant to nortriptyline, 75 mg/day. Over the last years he had begun to drink 60–90 ml of alcohol two to three times a week and to smoke cannabis almost daily, using up to 15 g weekly.

When Dr. C attempted to taper his dose of alprazolam, his anxiety increased. He did not take more than the prescribed dose but became tolerant to its effects and saved doses during the day to permit a higher one-time dose for effect. He became increasingly preoccupied with his alprazolam use. His wife was concerned about his use of cannabis and alprazolam, and there were increasing arguments about his use of these drugs. His work attendance suffered, and he was placed on job probation.

Three weeks before he sought medical assistance, Dr. C had started an 8-day self-prescribed tapering of alprazolam. Thirty-six hours after his last dose, he suffered two grand mal seizures. The evaluation, including a neurological examination, a CT scan of the head, an EEG, and a lumbar puncture, showed no abnormalities. The seizure was thought to have been a result of alprazolam withdrawal. Alprazolam, 1 mg t.i.d., was prescribed and Dr. C. was referred for further evaluation. He was admitted to our Alcoholism and Drug Dependence Unit, where the alprazolam was discontinued; phenobarbital therapy was begun and then tapered over 13 days. A maximum phenobarbital dose of 700 mg in one 24-hour period was required because of an increase in his vital signs.

Dr. C had a history of cannabis abuse (up to seven "joints" daily) and alcohol abuse (binge drinking on weekends) in high school, with poor school performance and an arrest for possession of marijuana. In high school he had also used LSD, peyote, mescaline, and amphetamines—all fewer than five times. He had used cocaine approximately five times, the last time 4 years previously. After his mother died, when he was 19, he had cut down his use of marijuana to two to three times monthly and did not continue his alcohol abuse, "pulling himself together" for college and medical school. His drug use had increased in the last year.

DISCUSSION

The behavioral aspects of drug dependence are reemphasized in *DSM-III-R,* which does not insist on tolerance or withdrawal as criteria for diagnosis. Several reports have implicated alprazolam as an addictive drug by describing a characteristic sedativelike withdrawal syndrome when use of the drug was discontinued. Our seven patients demonstrated this, and six of the seven (all but patient 4) demonstrated tolerance.

However, we were more concerned by the addictive behavior shown by most of the patients. All met criteria for alprazolam dependence as defined by the *DSM-III-R* criteria for psychoactive substance abuse (pp. 167–168). The patients' characteristics and the diagnostic requirements they fulfilled are summarized in table 1. All made attempts to cut down or stop using alprazolam but were unable to do so because of withdrawal-like anxiety symptoms. Probably most important, significant impairment in social and family life and occupational duties was clearly shown by four of the seven patients (patients 1, 2, 3, and 7). For two others, alprazolam appeared to cause disruption of important activities, because behavioral improvement was noted after use of the drug was tapered and discontinued, but underlying medical conditions and their treatment (patient 4 had a lymphoma and patient 5 an impairment in delayed recall) clouded the picture.

All but one of the patients were women. Their ages ranged from 27 to 53 years. All alprazolam use began during treatment prescribed for a variant of a depressive or anxiety syndrome. No patient claimed to have an illicit source of the drug; however, some patients were manipulative, increasing the dose against medical advice and obtaining drugs from multiple physicians or from a spouse's supply. One patient self-prescribed alprazolam, and months later his psychiatrist continued it.

The doses ranged from 2 to 12 mg/day. The duration of use was 6 months to 3 years. The proper duration of use of alprazolam has not been clearly established for its various indications. When depression is treated with conventional antidepressants, at least 6 months of treatment is recommended. However, with a benzodiazepine, withdrawal symptoms are likely to occur when the drug is stopped if usual doses are taken for more than 4 months (1–4), which happened in all of our cases.

It was rare to find "pure" alprazolam dependence. Six patients had a history of previous or concurrent use or abuse of alcohol, narcotics, marijuana, other benzodiazepines, or amphetamines (table 1). Two patients (patients 4 and 5) had used other benzodiazepines for long periods before using alprazolam. None was clearly abusing alcohol concurrently, but there was a history of probable alcohol abuse or

TABLE 1. Summary of Features of Seven Patients With Alprazolam Dependence

				Alprazolam Use		Other Substance Abuse or Use	
Patient	Sex	Age (years)	Manifestations of Dependence (*DSM-III-R* criterion numbers)[a]	Maximum Dose (mg/day)	Length of Use (years)	Previous	Concurrent
1	F	27	2–9	10	3.0	Probable alcohol abuse; amphetamine abuse	Sherry, 60–90 ml/night, for 2 months
2	F	38	2, 4–9	8	0.5	Probable alcohol abuse	None
3	M	31	2, 4–8	3	1.0	Alcohol and cannabis abuse; occasional use of LSD, peyote, amphetamines, mescaline, cocaine	Cannabis and alcohol
4	F	50	2, 5? (lymphoma obscured picture), 8, 9	2	2.0	Alcohol; diazepam, 6 mg/night, for 12 years	Triazolam, 0.5 mg/day
5	F	53	2, 5? (dementia obscured picture), 7, 8	5	2.0	Diazepam, 15 mg/day, for 13 years	None
6	F	51	2, 7, 8,	2	0.5	None	None
7	F	36	1–9	8–12	2.0	Alcohol; codeine	Codeine, 300–900 mg/day; triazolam, 6–8 mg/day

[a] The *DSM-III-R* criteria for psychoactive substance dependence (pp. 167–168) are, briefly summarized, as follows: 1) substance taken in large amounts or over a long time, 2) unsuccessful efforts to control use of substance, 3) much time spent in getting, taking, or recovering from effects of substance, 4) frequent intoxication or withdrawal symptoms at work, school, or home, 5) important activities given up or reduced because of substance use, 6) continued use of substance despite problems it causes, 7) marked tolerance for substance, 8) characteristic withdrawal symptoms present, 9) substance taken to relieve or avoid withdrawal symptoms.

dependence for five patients (patients 1, 2, 3, 4, and 7). Patient 1 had a history of amphetamine abuse. Patient 7 had a long history of narcotic abuse. Patient 3 had experimented with multiple street drugs and had a clear history of abuse of marijuana. However, in each case, we thought there was clear evidence of alprazolam abuse or dependence despite the presence of other drug abuse.

Even in relatively small doses, alprazolam may cause dependence if it is used long enough, which is similar to the experience with other benzodiazepines (1–4). This potential for dependence and addictive behavior should be considered when one makes the decision to prescribe alprazolam.

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Menstrual Cycle Phase-Related Changes in Appetite in Patients With Premenstrual Syndrome and in Control Subjects

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Menstrual cycle phase-dependent changes in appetite in women with premenstrual syndrome has not thus far been systematically demonstrated. In this study of 21 patients with premenstrual syndrome and 13 control subjects, there were significant increases in appetite in both groups, with a greater effect of menstrual cycle phase on appetite in the patients. Further, the premenstrual increase in appetite was highly correlated with self-ratings of mood (particularly depression) in the patients only. The authors discuss these findings with respect to endocrine influences on appetite regulation and potential implications for investigation of atypical depression.

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One of the most frequently described characteristics of premenstrual syndrome is alteration of appetite, with cravings for specific foods (1). This neurovegetative disturbance is one of a number of similarities between premenstrual syndrome and atypical depression that have been noted (2); in addition, it is of interest as a potential window into the physiological disturbances that underlie premenstrual syndrome. Despite frequent references to appetite disturbances associated with premenstrual syndrome, to our knowledge no systematic study of this relationship has been undertaken. However, several reports have suggested the existence of menstrual cycle phase-related changes in food intake in normal women, with increased intake observed during the luteal phase (3, 4). Variations in food intake have also been described as a function of reproductive endocrine cycle phase in several species of animals (5–9).

In this study, we sought to determine whether changes in appetite occur across the menstrual cycle and, furthermore, whether changes in appetite correlate with mood changes reported by patients with premenstrual syndrome. We therefore evaluated daily self-ratings of appetite throughout the menstrual cycle in patients with well-defined premenstrual syndrome as well as in control subjects.

METHOD

For this investigation we selected 21 women (mean±SD age=37.3±5.3 years) who showed prospectively confirmed premenstrual mood changes after 3 months of self-ratings, namely, at least a 30% increase in mean negative mood symptom ratings in the 7 days preceding menses compared with the 7 days following cessation of menses (10). These women participated in a study of the biology of premenstrual syndrome and were initially recruited through a description of the study in the local newspaper, which solicited the participation of women who were in their reproductive years and in good health, who were taking no medications, and who were experiencing menstrually related mood or behavioral changes. In addition, all of these women met diagnostic guidelines for premenstrual syndrome (NIMH Workshop on Premenstrual Syndrome, Rockville, Md., April 14–15, 1983) as well as criteria for periluteal phase dysphoric disorder (1983 draft of *DSM-III-R*).

The comparison (control) group consisted of 13 subjects (mean±SD age=32.2±8.5 years) who gave no evidence of any menstrually related mood disorder during 2 months of prospective mood self-ratings. These control subjects were recruited through the National Institutes of Health normal-volunteer office. Potential subjects who had a current medical illness or a psychiatric illness assessed by the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (11) were excluded. Three of the control subjects had a psychiatric history of situational adjustment disorder, and among the patients three had histories of single episodes of major depressive disor-

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der, two had had generalized anxiety disorder, one had had panic disorder, and one had had bulimia. The gynecological histories of both the patients and the control subjects were unremarkable; the mean±SD menstrual cycle length was 29.55±2.95 days (range=26–35) for the patients and 29.11±3.52 days (range=24–35) for the control subjects. All of the subjects were medication free and were taking no oral contraceptives or psychotropic medications.

All subjects completed the 21-item Premenstrual Assessment Form of Daily Ratings (12) over a time period ranging from 2 to 9 months. The total number of evaluated months was 78 for the 21 patients with premenstrual syndrome and 30 for the 13 control subjects. The assessment form measures somatic and mood symptoms on a severity scale from 1 to 6. Because of our interest both in the relationship between menstrual cycle phase and appetite and in the relationship between mood and appetite, we examined five items from the daily rating form: appetite, depression, anxiety, irritability, and feelings of loneliness. For purposes of analysis, mean severity scores were calculated for each of the variables for the 7 days before the onset of menses (premenstrual phase) and the 7 days after the cessation of menses (postmenstrual phase).

The relationships between menstrual cycle and appetite in patients and control subjects were analyzed by analysis of variance with repeated measures; menstrual cycle phase and group (patient or control) were the independent variables. The relationships between appetite and mood were examined by means of Pearson product-moment correlation coefficients and multiple regression analysis in order to identify the mood variable or combination of variables that accounted for a significant part of the variance in appetite. This analysis was performed by group and menstrual cycle phase.

RESULTS

The first part of the analysis, which used the multivariate approach to repeated measures, showed significant effects for menstrual cycle phase (F=31.39, df=1, 32, $p<0.0001$), group (F=5.12, df=1, 32, $p<0.05$), and the interaction between group and menstrual cycle phase (F=15.51, df=1, 32, $p<0.0005$). In the premenstrual phase of the cycle, the mean±SD appetite rating in the premenstrual syndrome group (3.69±1.40) was significantly higher than that of the control group (1.97±0.69) (t=3.32, df=32, $p<0.005$). In addition, the premenstrual syndrome group's mean±SD appetite rating in the premenstrual phase was significantly higher than its rating in the postmenstrual phase (1.32±0.44) (paired t=6.20, df=20, $p<0.0001$). The control group showed a similar pattern: its mean±SD rating in the premenstrual phase (1.97±0.69) was significantly higher than its rating in the postmenstrual phase (1.62±0.62) (paired t=3.63, df=12, $p<0.0005$). However, the premenstrual increase in appetite in the premenstrual syndrome group was significantly greater than that in the control group, as evidenced by the significant Group by Menstrual Cycle Phase interaction on repeated measures analysis. Analysis of mean appetite ratings for both groups in the postmenstrual phase of the cycle revealed no significant differences between the two groups.

TABLE 1. Correlations Between Appetite and Mood in Premenstrual Syndrome Patients and Control Subjects

Group	Correlation With Appetite (r)			
	Depression	Anxiety	Irritability	Loneliness
Premenstrual syndrome (N=21)				
7 days preceding onset of menses	0.82[a]	0.62[b]	0.68[c]	0.60[b]
7 days following end of menses	0.30	0.32	0.34	0.17
Control (N=13)				
7 days preceding onset of menses	0.20	0.16	0.23	-0.13
7 days following end of menses	0.28	0.03	0.01	-0.16

[a] $p<0.001$.
[b] $p<0.05$.
[c] $p<0.01$.

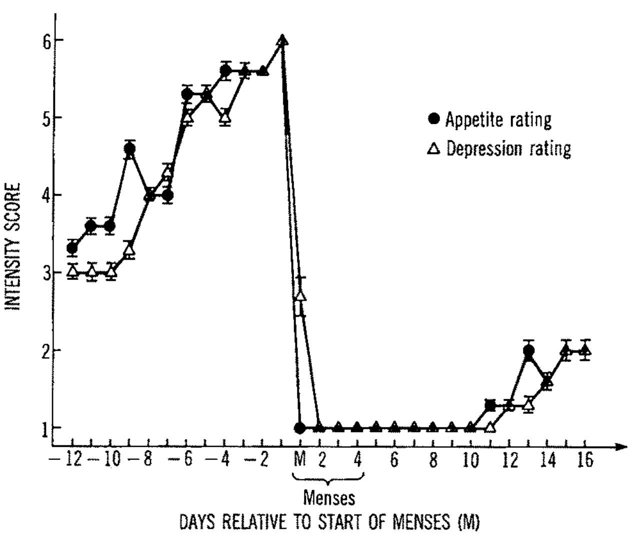
The second part of the analysis demonstrated that the correlation coefficients between mood and appetite were highly significant for the premenstrual syndrome group in the premenstrual phase but not significant in the postmenstrual phase; no significant relationship appeared for the control subjects in either menstrual phase (see table 1). An example of the relationship between changes in appetite and depressed mood in a patient with premenstrual syndrome is shown in figure 1.

Multiple regression analysis revealed that the mood measures accounted for a significant part of the variance in appetite for the premenstrual syndrome group in the premenstrual phase only ($r^2=0.70$, df=16, $p<0.0005$) (postmenstrual phase: $r^2=0.15$, df=20, $p=0.57$). For depression, $r^2=0.65$, df=20, $p<0.001$, with only an additional 9% contributed by including anxiety, irritability, and feelings of loneliness in the regression model. The regression analysis for the control subjects revealed an insignificant r^2 in both phases (premenstrual phase: $r^2=0.15$, df=8, $p=0.83$; postmenstrual phase: $r^2=0.11$, df=8, $p=0.88$).

DISCUSSION

By using concurrent, longitudinal daily ratings, we were able to show a dramatic increase in appetite in premenstrual syndrome patients during the premenstrual phase of the cycle. (The need for prospective assessment of symptom occurrence and timing in patients with premenstrual syndrome has been stated elsewhere [10, 13].) In addition, we found a highly

FIGURE 1. Menstrual Cycle-Related Changes Over 7 Months in the Mean±SD Self-Ratings of Appetite and Mood in a Patient With Premenstrual Syndrome



significant relationship between appetite and mood in patients in the premenstrual phase of the cycle only. Control subjects showed no evidence of any relationship between appetite and mood in either phase. Interestingly, the control subjects also demonstrated an increase in appetite in the premenstrual phase, albeit a smaller increase than that observed in the patients.

These data raise several questions. 1) Why does appetite appear to increase during the premenstrual phase? 2) Why is the premenstrual increase in appetite greater in premenstrual syndrome patients than in control subjects? 3) What is the significance of the relationship between mood and increase in appetite in patients with premenstrual syndrome?

It has been observed by a number of investigators (5–9) that food intake in several species varies with the stage of the ovulatory cycle. The food intake of cycling rats and primates appears to vary inversely with plasma estradiol levels; it diminishes greatly at estrus or around the time of ovulation and increases at diestrus and in the luteal phase of the menstrual cycle (6). Since food intake is lowest at the time of maximal estradiol concentrations, it appears that estradiol may have an inhibitory effect on food intake. Data supporting this hypothesis can be found in studies of female rhesus monkeys (7, 8) that have shown a coincidence of high food rejection and high estradiol levels around the time of ovulation and a coincidence of low food rejection and low levels of estradiol in the early luteal phase. Further, it has been observed in rhesus monkeys as well as in baboons that food intake is significantly greater in the midluteal phase than in the early to midfollicular phase of the menstrual cycle. However, these findings might also suggest that progesterone plays a role in the regulation of appetite (6, 9, 14). Since progesterone is elevated during the midluteal phase, it may have a stimulating effect on appetite (9) or may antagonize the ability of estradiol to suppress appetite (3). These hypotheses are at present unproved. Finally, consistent with our findings as well as those appearing in the animal literature, two studies of women (3, 4) have demonstrated an increase in food intake in the postovulatory or luteal phase compared with the preovulatory follicular phase.

The mechanisms by which hormonal changes during the menstrual cycle may affect the regulation of appetite remain to be elucidated, although they may include secondary effects on central neurotransmitter systems implicated in appetite regulation. For example, it has been suggested that estradiol inhibition of dopamine β-hydroxylase (15) decreases brain norepinephrine, an apparent stimulant of appetite (6).

If the considerable increase in appetite of our control subjects in the premenstrual phase can be regarded as a normal biological event, then the much higher increase in appetite of the patients might be considered an abnormal response or oversensitivity to normal biological stimuli (paper by G.R. Merriam et al. presented at the NIMH Workshop on Premenstrual Syndrome, Rockville, Md., April 14–15, 1983). Alternatively, the biological abnormalities that have been hypothesized to underlie premenstrual syndrome may mediate the menstrual cycle phase-related differences in appetite. For example, exaggerated fluctuations of plasma β-endorphin, a peptide with purported stimulating effects on appetite (16), have been reported in patients with premenstrual syndrome (17). However, the decreased luteal phase β-endorphin levels described in that study are not consistent with the increased appetite that we observed.

Our findings that increase in appetite was significantly and highly correlated with mood in the premenstrual syndrome patients during the premenstrual phase but not in the control subjects suggests that the major changes in mood reported by the patients but not by the control subjects may have contributed to the large premenstrual increase in appetite of the premenstrual syndrome patients. In this regard, premenstrual syndrome appears similar to atypical depression, since both disorders are characterized by depressive symptoms and increased appetite (18–20). The similarity of these two disorders has been previously noted (2). Further, the appetite disturbance in these disorders may provide a clue to their pathophysiology. For example, it has been suggested that carbohydrate craving reflects a compensatory attempt to provide the brain with the substrate (tryptophan) necessary to correct a serotonin deficiency (21). Since dysregulation of serotonin may be linked to depression (22), the appetite and mood alterations noted in premenstrual syndrome and atypical depression may be the products of a common central neuroregulatory disturbance. Finally, it is possible, as suggested elsewhere (23), that the menstrual cycle acts as a *zeitgeber* which directs or choreographs changes in mood state and thereby facilitates transition into (rather than causes) an atypical depression state characterized by mood and appetite disturbances.

This study showed in a prospective fashion that appetite, menstrual cycle phase, and mood are clearly related. These findings not only confirm anecdotal reports of appetite dysregulation in patients with premenstrual syndrome but also suggest that further longitudinal study of appetite and mood in relation to endocrine change in the reproductive system may enhance our understanding of the physiological changes that underlie atypical depressive states.

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Anxiogenic Effects of Caffeine on Panic and Depressed Patients

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Caffeine increases anxiety in people with anxiety disorders. To determine whether caffeine exerts a similar effect in depression, the authors compared retrospective reports of caffeine intake and symptoms produced by caffeine ingestion in patients with panic disorder, patients with major depression, and control subjects. Panic patients consumed less caffeine and reported more symptoms than depressed or control subjects. Although depressed patients did not differ from control subjects in caffeine intake or most symptoms, more depressed patients reported that caffeine induced anxiety. These data support prior reports that panic patients have increased sensitivity to caffeine; some depressed patients may also have increased sensitivity.

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The anxiogenic effects of caffeine are well documented (1–4). We reported previously that anxious patients consume significantly less caffeine than normal control subjects, presumably because of this anxiogenic effect (5). In contrast, it has been suggested that certain subgroups of depressed patients *increase* their daily caffeine intake while depressed (6), possibly as an attempt to improve mood. Although some depressed patients may use caffeine to improve mood, Greden et al. (7) reported that the daily caffeine intake of a sample of psychiatric inpatients was similar to that of nonpsychiatric inpatients. Boulenger et al. (8, 9) also reported no difference in caffeine consumption between patients with major depression and normal control subjects or between patients with panic disorder and normal control subjects (although the panic patients did show a tendency to use less caffeine, and significantly more panic patients than control subjects had stopped drinking coffee completely).

In addition to a lower daily caffeine intake, greater sensitivity to caffeine in people with panic disorder has been shown by direct caffeine challenge (3, 4) and has also been observed in questionnaire studies (5, 8, 9). However, Boulenger et al. (8, 9) reported no greater sensitivity to caffeine in people with major depression. Nevertheless, the question of whether depressed individuals have a greater sensitivity to an anxiogenic agent has heuristic interest because of the substantial overlap between anxiety and depressive disorders (4, 10–13).

These prior studies suggest that panic patients use less caffeine daily than normal control subjects and have a greater sensitivity to caffeine's anxiogenic effects, while patients with major depression use amounts of caffeine similar to those used by normal control subjects and show no greater sensitivity. However, to evaluate both intake and sensitivity to caffeine's anxiogenic effects, direct comparisons of these three diagnostic groups are necessary. Thus, we examined retrospective reports of daily caffeine intake and profiles of self-reported symptoms ("sensitivity") in response to caffeine intake in people with panic disorder or major depression and in control subjects hospitalized for nonpsychiatric reasons, using the same rating instrument in all three groups. We used this direct comparison to determine whether depressed patients, in addition to panic patients, show a lower daily intake and/or greater sensitivity than control subjects.

METHOD

The 127 depressed patients had been diagnosed as having major depressive disorder with the Research Diagnostic Criteria (14); their mean age was 41 years, and the group included 44 men and 50 inpatients. The 30 patients with panic disorder had been diagnosed according to *DSM-III* and were all outpatients; the group had a mean age of 35 years and included nine men. The control subjects were 124 hospitalized patients with nonpsychiatric illnesses; this group had a mean age of 40 years and included 39 men. All subjects

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TABLE 1. Distribution of Self-Reported Caffeine Consumption in Patients With Depression or Panic Disorder and Normal Control Subjects[a]

Daily Caffeine Consumption	Major Depressive Disorder (N=127)		Panic Disorder (N=30)		Control Subjects (N=124)	
	N	%	N	%	N	%
Low (0–249 mg)	64	50	27	90	51	41
Moderate (250–749 mg)	39	31	2	7	53	43
High (≥750 mg)	24	19	1	3	20	16

[a] Difference overall: $\chi^2=25.01$, df=4, $p<0.001$; panic versus depression: $\chi^2=16.79$, df=2, $p<0.001$; panic versus control: $\chi^2=23.87$, df=2, $p<0.001$.

gave informed consent. They completed our caffeine questionnaire (available on request), which retrospectively assesses daily caffeine intake from 25 sources, and self-ratings of symptom responses to drinking one cup of coffee. The self-rated symptoms were statements such as "makes me anxious," which were each rated on a 5-point scale, "strongly agree" to "strongly disagree." If a subject answered "strongly agree" or "somewhat agree," the symptom was rated as present. Daily caffeine intake was based on the daily use before hospitalization.

Daily caffeine intake was categorized according to previously reported levels: low consumption, 0–249 mg/day; moderate consumption, 250–749 mg/day; high consumption, ≥750 mg/day (5, 7, 15). We compared the symptomatic responses to drinking a cup of coffee of only the subjects with low consumption in the three diagnostic groups (panic, depression, control) because almost all of the panic patients had low consumption (see Results). Depression was further examined after dividing the depressed patients into unipolar and bipolar subgroups. Chi-square analysis was used for all data analyses; the p value required for significance was ≤0.0045 (i.e., 0.05/11, by Bonferroni adjustment). Because Bonferroni adjustments produce conservative cutoff values for significance testing, p values between 0.0045 and 0.025 are reported here as "trends."

RESULTS

The mean±SD self-reported daily caffeine intake was 120±203 mg for the panic patients and 393±415 mg for the depressed patients; the mean intake of the control subjects was 385 mg (approximation calculated from the distribution among the three consumption groups). The panic patients reported significantly less caffeine use than either the depressed patients or the control subjects (table 1). Indeed, 90% of the panic patients had low caffeine consumption, and two-thirds used less than 100 mg/day. The percentages for the depressed patients were not significantly different from those for the control subjects ($\chi^2=3.72$, df=2, n.s.). When the depressed group was divided into unipolar and bipolar patients, there was no significant difference in daily caffeine consumption between the bipolar (52% low, 29% moderate, 19% high) and unipolar (49% low, 32% moderate, 19% high) patients ($\chi^2=0.94$, df=2, n.s.).

Among only the subjects with low caffeine consumption, anxiety in response to caffeine ingestion was reported by significantly more panic patients than control subjects, and a similar trend was observed in the comparison of panic and depressed patients (table 2). Tachypnea was significantly more frequent in the panic patients than in the depressed subjects, and similar trends were observed for palpitations and tachycardia; the differences in these symptoms between the panic patients and control subjects did not reach statistical significance (table 2). On the other hand, the depressed patients did not report more symptoms than the control subjects; there was a tendency for more of the depressed patients to report anxiety, but this difference did not reach statistical significance ($\chi^2=4.16$, df=1, $0.025<p<0.05$) (table 2). When the total samples of depressed patients (N=127) and of control subjects (N=124) (i.e., all levels of caffeine consumption) were compared, a strong trend toward a significantly higher prevalence of anxiety responses in the depressed patients was observed ($\chi^2=9.52$, df=1, $p<0.01$).

TABLE 2. Retrospective Self-Reports of Symptom Responses to Caffeine in Patients With Depression or Panic Disorder and Normal Control Subjects Who Had Low Caffeine Consumption[a]

Symptom	Major Depressive Disorder (N=64)		Panic Disorder (N=27)		Control Subjects (N=51)	
	N	%	N	%	N	%
Anxiety[b]	24	37.5	21	77.8	[illegible]	21.6
Diarrhea	6	9.4	3	3.7	[illegible]	15.7
Diuresis	45	70.3	20	74.1	[illegible]	58.8
Headache	3	4.7	3	11.1	[illegible]	13.7
Lightheadedness	10	15.6	5	18.5	[illegible]	13.7
Palpitations[c]	11	17.2	13	48.2	[illegible]	25.5
Stomachache	10	15.6	8	29.6	[illegible]	27.5
Spot in front of eye	2	3.1	1	3.7	[illegible]	3.9
Tachycardia[d]	14	21.9	14	51.9	[illegible]	27.5
Tachypnea[e]	3	4.7	8	29.6	[illegible]	11.8
Tremulousness	15	23.4	10	37.0	[illegible]	15.7

[a] An overall chi-square analysis was performed across all three groups for each variable. If significant ($p\leq0.0045$; i.e., [illegible].05/11, by Bonferroni adjustment), a separate analysis for each combination of groups was performed. Values indicating trends (0.0045<p<0.025) are also presented.

[b] Overall: $\chi^2=23.54$, df=2, $p<0.001$; panic versus depression: $\chi^2=9.73$, df=1, $p<0.01$; panic versus control: $\chi^2=23.$[illegible]4, df=1, $p<0.001$.

[c] Overall: $\chi^2=7.46$, df=2, $p<0.025$; panic versus depression: $\chi^2=6.97$, df=1, $p<0.02$.

[d] Overall: $\chi^2=8.36$, df=2, $p<0.025$; panic versus depression: $\chi^2=9.01$, df=1, $p<0.01$.

[e] Overall: $\chi^2=11.21$, df=2, $p<0.01$; panic versus depression: $\chi^2=12.95$, df=1, $p<0.001$.

TABLE 3. Retrospective Self-Reports of Symptom Responses to Caffeine in Patients With Bipolar or Unipolar Depression and Normal Control Subjects[a]

	Bipolar Depression (N=31)		Unipolar Depression (N=96)		Control Subjects (N=124)	
Symptom	N	%	N	%	N	%
Anxiety[b]	13	41.9	35	36.5	24	19.4
Diarrhea	7	22.6	7	7.3	26	21.0
Diuresis	26	83.9	72	75.0	81	65.3
Headache	1	3.2	4	4.2	12	9.7
Lightheadedness[c]	9	29.0	7	7.3	10	8.1
Palpitations	9	29.0	12	12.5	24	19.4
Stomachache	6	19.4	15	15.6	22	17.8
Spot in front of eye	1	3.2	2	2.1	6	4.8
Tachycardia	12	38.7	21	21.9	24	19.4
Tachypnea	3	9.7	3	3.1	13	10.5
Tremulousness	6	19.4	21	21.9	22	18.6

[a] An overall chi-square analysis was performed across all three groups for each variable. If significant ($p \leq 0.0045$; i.e., 0.05/11, by Bonferroni adjustment), a separate analysis for each combination of groups was performed. Values indicating trends ($0.0045 < p < 0.025$) are also presented.

[b] Overall: $\chi^2=10.77$, df=2, $p<0.01$; bipolar versus control: $\chi^2=8.23$, df=1, $p<0.01$; unipolar versus control: $\chi^2=7.76$, df=1, $p<0.02$.

[c] Overall: $\chi^2=13.32$, df=2, $p<0.005$; bipolar versus unipolar: $\chi^2=9.56$, df=1, $p<0.01$; bipolar versus control: $\chi^2=9.07$, df=1, $p<0.01$.

Table 3 compares the symptomatic responses to caffeine of the bipolar and unipolar depressed patients and the control subjects. The percentages of depressed patients reporting anxiety were similar, but the frequency in each group was higher than that in the control group, as was the case for the total sample of depressed patients. The bipolar patients reported more lightheadedness than either the unipolar patients or the control subjects.

DISCUSSION

In this study panic patients consumed less caffeine than nonpsychiatric patient control subjects or depressed patients, and the intake of the depressed patients was the same as that of the control subjects. The panic patients reported more anxiety in response to caffeine than the control subjects or depressed patients, and the depressed patients showed a tendency to report more anxiety than the control subjects. Cardiac and respiratory symptoms in response to caffeine ingestion were more frequent in the panic patients as well, suggesting abnormal autonomic reactivity (16).

The retrospective data collection for the three patient groups reported here (depressed patients, medical control subjects, and panic patients) began at different times; the collection for the depressed patients started a decade earlier than for the panic patients, and for the medical control subjects it began fairly soon after the beginning of data collection for the depressed patients. Even though the same instrument was used for all subjects, the possibility that this difference in timing might influence these results must be considered when interpreting the outcome of this study. However, total daily caffeine intake in the United States did not change significantly during the entire period of data collection (17). Additionally, even though all of the inpatients were instructed to rate caffeine intake and symptoms before hospitalization, it is possible that inpatients might be different from outpatients. We compared the hospitalized depressed patients to the depressed patients who had not been hospitalized; we found no significant differences in either their reports of caffeine intake or their anxiety scores (18).

The panic patients reported the greatest sensitivity to caffeine's anxiogenic and other symptom effects. This is likely to be a major reason for their lower daily caffeine intake. These data are consistent with those from studies involving direct caffeine challenge, in which panic patients experienced greater increases in anxiety symptoms than did control subjects (3, 4), and suggest that retrospective ratings can be used reliably to determine caffeine intake and caffeine-induced symptoms.

Although fewer of the patients with major depressive disorder than panic patients reported anxiety responses to caffeine, caffeine caused anxiety in more depressed patients than medical control subjects; the bipolar patients were not significantly different from the unipolar patients in this regard. This greater sensitivity to caffeine's anxiogenic effect in patients with major depressive disorder was different from the finding of Boulenger et al. (8, 9), who reported no difference between patients with major depression and normal control subjects; this discrepancy may be due to their smaller sample. Also, Boulenger et al. used healthy control subjects instead of nonpsychiatric medical patients, which might have influenced the results of these comparisons of depressed patients to normal subjects. This greater sensitivity to caffeine's anxiogenic effect in both panic disorder and major depression suggests another biological similarity between these two disorders. It does not, of course, exclude the possibility that this similarity is due to a subgroup of depressed patients who have a mixed anxious-depressive syndrome; indeed, this seems likely.

Daily caffeine intake and responses to caffeine's anxiogenic effect were not different between our bipolar and unipolar depressed patients. However, lightheadedness was more common among the bipolar depressed patients than among the unipolar depressed patients or medical control subjects; palpitations and tachycardia showed tendencies in the same direction. Further study is required to determine whether the difference in symptom response to caffeine between bipolar and unipolar depressed patients is reliable, and if so, if the symptom difference is related to a difference in pathophysiology.

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Response to Memory Training and Individual Differences in Verbal Intelligence and State Anxiety

Jerome A. Yesavage, M.D., Javaid Sheikh, M.D., Elizabeth Decker Tanke, Ph.D., and Robert Hill, Ph.D.

Prior studies have documented the effectiveness of several types of memory training for the elderly with normal age-related memory losses. Despite these positive results, there is substantial variability of individual response to treatment. The authors describe attributes of individuals most likely to benefit from two types of memory training. They found that for 40 elderly volunteers performance on the WAIS vocabulary subscale correlated with response to a treatment combining mnemonics and verbal elaboration techniques and scores on the Spielberger State-Trait Anxiety Inventory correlated with response to a treatment combining mnemonics and relaxation techniques.

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In a series of prior studies (1–3), we have documented the effectiveness of several types of memory training for elderly persons with normal age-related memory losses. Despite these positive results, we find substantial variability of individual response to treatment. Some subjects show much improvement while others show little change at all. The present study reports within-group analyses of two successful treatments and suggests attributes of individuals most likely to benefit from each type of training.

Elderly persons who score in the normal range on cognitive function tests may have considerable decline in function from their performance when they were younger. For example, norms on the verbal measures of the commonly used WAIS decline 13%–30% from ages 20–34 years to ages 70–74 years, and declines between the same age groups on WAIS performance measures range from 25% to 64% (4). Some argue that these deficits reflect slowed motor performance on timed tests (5); however, a study in which five timed WAIS subtests were administered with unlimited time to elders (6) showed that performance decrements were reduced in only one of the five tests. Although some (7–10) have cautioned against drawing conclusions from cross-sectional data that may reflect cross-generational differences rather than age-related differences, a 21-year longitudinal study (11) documented declines of 10%–38% on a battery of intelligence measures. Another study of nonverbal memory (12) demonstrated, in both longitudinal and cross-sectional samples, that performance on the Benton Visual Retention Test declines substantially with age. Craik's classic review of memory and aging (13) and Poon's extensive recent review (14), which reviews 19 other reviews, lists a wide variety of significant and substantial declines in memory function in young versus old normal in individuals. These declines were noted on virtually all the subscales on the Guild Memory Test, paired associates, and memory for prose passages. Despite these cautions and several areas in which memory function is preserved with aging, Poon concludes that "... substantial differences are found in the acquisition and retrieval of new information from secondary memory" (p. 455).

Several experimenters (15–18) have attempted to improve memory function in the elderly by teaching them to use psychological techniques, especially mnemonics. However, the results of studies in which standard mnemonics based on image associations were used have been disappointing. Our approach has emphasized the combination of image association mnemonics with techniques that have been designed to overcome certain obstacles to mnemonics use common in the elderly, such as the inability to form clear and elaborate visual image associations or performance anxiety.

A number of studies (19–21) have shown that instructions which increase elaboration of processing facilitate retention of visual materials in the young and the old. For example, recognition memory for faces is improved by requiring subjects to make semantic judgments about faces as they are viewed. Such findings indicate that processing a stimulus in additional, nonredundant ways may make it more likely to be

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remembered later (22, 23). Taking this line of reasoning a step further, one study (3) examined the effectiveness of certain instructions designed to increase elaboration of processing of visual image associations used in a mnemonic device. Groups of elderly subjects were taught to learn name-to-face associations using different techniques. Control group subjects were taught a standard name-face mnemonic: select a prominent facial feature, transform the surname into a concrete word for each name-face pair, and use interactive imagery to form an association between the prominent feature and the transformed name. The active treatment group was given the same instructions except that these subjects were also taught to judge the pleasantness of the image association that was formed. As predicted, improvement following instruction was minimal when no judgment was performed but strong when the judgment was also applied. In the current study, we used this technique to test whether verbal intelligence relates to ability to benefit from such therapy.

Changes in attention have been less studied in the aged than changes in memory per se, but they may have substantial importance in explaining memory and other cognitive changes with age (24). Few studies have examined the role of anxiety as a factor impairing attention in the elderly (25). In younger subjects, however, data suggest that higher anxiety levels are associated with less reliable recall of eyewitness testimony (26) and that high anxiety levels impair test performance (27). This may be a general phenomenon: high levels of anxiety, arousal, or depression produce distraction and reduce cognitive capacity and performance (25). The second treatment we studied combined mnemonic training with an anxiety reduction technique. We tested whether initial anxiety levels relate to ability to benefit from this therapy.

Despite the positive results noted in the two treatments we studied, substantial variability in response to treatment remains unexplained. Could it be that individual characteristics of subjects make them more likely to benefit from one therapy than another? We examined the effectiveness of two standard psychometric scales in predicting response to treatment in normal elderly subjects receiving two types of treatment. We hypothesized that subjects with relatively high scores on a measure of verbal intelligence such as the WAIS vocabulary scale would do relatively well in training to increase verbal elaboration while those with relatively high scores on a measure of anxiety such as the state portion of the Spielberger State-Trait Anxiety Inventory (28) would do relatively well in training to reduce performance anxiety.

METHOD

Volunteers solicited through radio and newspaper advertisements, through referrals from the Palo Alto Senior Center, and from local physicians were asked to participate in memory training. The subjects (N=40) were randomly assigned to one of two training groups. Since it was not feasible to study the groups simultaneously, groups of four to six subjects were studied sequentially in random order until a total of 20 subjects in each group was achieved. The subjects were randomly assigned to one of the two training groups within each treatment block, and then assignments were repeated for another treatment block, and so on. Each treatment block consisted of five consecutive steps: 1) a baseline name-face recall test (test 1), 2) a pretraining period previously shown to improve response to training in the use of a mnemonic device for name-face recall, 3) a repeat of the name-face recall test (test 2), 4) a training period in the use of a mnemonic device, and 5) another repeat of the name-face recall test (test 3). The major dependent variable was face-name recall. Comparable forms with 12 name-face pairs were randomly assigned to each testing session. The details of the testing have been described elsewhere (3).

Group 1 received pretraining in the application of a judgment technique. Specifically, subjects were taught to form visual image associations between a prominent feature on the face and a concrete transformation of the name and then asked to judge whether the images were pleasant or unpleasant. The verbal elaboration pretraining involved 1) teaching the subjects visual imagery (the main mnemonic technique is a visual technique) and then 2) teaching them in a Socratic method to continually pose verbal questions about the images. In studies on levels of processing a number of different questions have been suggested; e.g., "Does this look like an honest face?" In our technique, we stress the question, "Is the association pleasant?" The training also includes such other questions as "Is the association silly?" "Does the association make sense . . . does the name transformation fit the prominent feature or not?" "Is the association logical?" The subjects are taught to be verbally critical, i.e., to ask critical questions about the association. Group 2 received progressive relaxation pretraining to diminish anxiety levels before learning the standard mnemonic. Each group received a total of 14 hours of instruction (pretraining and mnemonic training) over 2 weeks, and psychometric testing of each subject was performed before the start of training.

Student's t tests revealed no significant demographic differences between the two groups. The average age of the 40 subjects was 67 years (range, 60–85 years). Nine (45%) of the subjects in group 1 and 11 (60%) of the subjects in group 2 were men. The average educational level of the 40 subjects was the equivalent of 2 years of college. Their mean±SD scores were 2.23±1.83 on the Geriatric Depression Scale (29) (indicating little depression), 34.90±8.10 and 34.22±11.06 on the state portion of the Spielberger State-Trait Anxiety Inventory (indicating moderate anxiety), and 50.20±10.36 and 51.48±5.78 on the WAIS vocabulary subscale for groups 1 and 2, respectively.

TABLE 1. Name-Face Recall Scores of 40 Elderly Volunteers Given One of Two Treatments to Improve Memory

	Raw Score								
	Test 1 (baseline)		Test 2 (after pretraining)		Test 3 (after training)		Change Score[a]		
Treatment Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Improvement (%)[b]
Group 1—judgment pretraining, mnemonic training (N=20)	3.18	2.77	4.63	2.98	6.68	3.25	3.50	2.68	110
Group 2—relaxation pretraining, mnemonic training (N=20)	3.58	2.81	4.53	3.51	6.25	3.14	2.68	2.92	75

[a] Test 3 score minus test 1 score.

[b] Test 3 score minus test 1 score divided by test 1 score multiplied by 100.

RESULTS

The results of our study are presented in table 1. Data analysis was based on a measure of improvement in name-face recall performance from the baseline test (test 1) to the final posttest period (test 3). Because of potential artifacts that may be introduced by using change scores, the analyses we report were replicated with regression models (30) and similar results were obtained. We present the change score data for ease of interpretability. Correlations of change scores with age were nonsignificant (−0.30 and −0.01 for groups 1 and 2, respectively). Correlations of change scores with educational level were also nonsignificant (0.13 and 0.07, respectively). Correlations between WAIS scores and anxiety scores were nonsignificant overall and for each group individually.

We performed within-group correlational analyses of the Spielberger anxiety inventory and the WAIS vocabulary subscale scores with improvement in recall. The regression analyses follow methods of Cronbach and Snow (30) and the theory of Attribute Treatment Interactions, which are commonly used in educational psychology to describe interactions between attributes of certain students and educational methods. Our original hypotheses stated that subjects with relatively high scores on a measure of verbal intelligence such as the WAIS vocabulary subscale would do relatively well in training to increase verbal elaboration while those with relatively high scores on a measure of anxiety such as the Spielberger State-Trait Anxiety Inventory would do relatively well in training to reduce performance anxiety. To test these hypotheses we calculated product-moment correlations between WAIS scores and change scores in name-face recall within the two treatment groups (31). A correlation of 0.38 ($df=18$, $p<0.05$, one-tailed) was obtained within group 1, and a correlation of −0.47 ($df=18$, $p<0.05$, one-tailed) was calculated within group 2, accounting for 14% and 22% of variance within the respective treatment group.

The WAIS vocabulary subscale score was also regressed against change in memory performance scores for each treatment group, and an interaction was suggested; those with higher WAIS vocabulary scores performed better in training group 1 (judgment/mnemonic), but those with lower scores did better in training group 2 (relaxation/mnemonic). As in previous studies (2), a significant correlation between anxiety scores and performance on the relaxation pretraining (group 2) was found ($r=0.38$, $df=18$, $p<0.05$, one-tailed). The correlation of anxiety scores and performance on the judgment pretraining (group 1) was negative ($r=-0.40$, $df=18$, $p<0.05$, one-tailed). These account for 14% and 16% of variance within the respective group.

DISCUSSION

Our data support the hypotheses that subjects who scored relatively high on a measure of verbal intelligence would do relatively well in training to increase verbal elaboration while those scoring relatively high on a measure of anxiety would do relatively well in training to reduce performance anxiety. These findings may explain why some subjects do better in one type of instruction than others and why similar training programs that do not take individual differences into account have modest results. Such results might lead to assignment of subjects on the basis of their initial psychometric scores to the treatment that would bring them the best results.

There are other factors that should be explored as potential predictors of response. Work in cognitive training to improve other intellectual functions suggests that an a priori familiarity with the criterion task is associated with improvement, as is external locus of control in highly structured instructional settings (15). Willis (15) also suggests that the high variability of response may be due to other nonspecific factors as well: how the materials are organized, utilization of examples, redundancy of information, monetary and social reinforcement, and prior performance success. Thus, there are a number of other potential predictors of response and sources of variance that might be considered in future studies.

Increasing interest in cognitive retraining for the elderly is likely. Elders who want to continue to work as long as possible may be appropriately concerned if these normal losses lead to reduced professional abilities or social embarrassment. In response to the increasing numbers of elderly with such complaints, the problem was discussed in depth at a series of meetings sponsored by NIMH, and it was suggested that these losses be formally termed minimal memory impairment. Such official recognition should increase the attention paid to this problem, and the increased attention paid to individual differences of elders with minimal memory impairment should lead to more effective therapies.

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Book Forum

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NEUROPSYCHIATRY AND NEUROPSYCHOLOGY

Studies in Neuropsychology: Selected Papers of Arthur Benton, *edited by Louis Costa, Ph.D., and Otfried Spreen, Ph.D. New York, Oxford University Press, 1985, 341 pp., $39.50.*

Volumes of collected papers (Festschriften, for example) usually are celebrations of an individual, contain seriously dated material, and, at best, are destined to a dusty shelf life in libraries. Is there any reason to expect that *Studies in Neuropsychology,* containing selected papers of the eminent neuropsychologist Arthur Benton, will be different?

The answer to this question is a resounding yes, even though it does have all of the attributes noted above. It celebrates an individual, Arthur Benton, a highly respected major figure in neuropsychology both in the United States and throughout the world. The volume does contain dated material (the oldest was published more than 30 years ago); however, the editors, both neuropsychologists at the University of Victoria, have included a number of recent papers, including two never published before. And it can be anticipated that this volume will have a place on medical library shelves throughout the world for many years to come.

The answer to the original question remains yes for a number of pertinent reasons. In the first place, Arthur Benton is not only a neuropsychologist but must also be ranked among the foremost historians in the field. The historical papers contained in this volume are timeless and represent valuable records of neuropsychology. Benton was one of the earliest practitioners and one of the major developers of this field. *Studies in Neuropsychology* contains excellent examples of this development. Beyond that, Benton was an innovator, particularly in the scientific design of research for use in subjects with brain damage. Many of the papers contained in this volume are seminal presentations in neuropsychology and warrant careful attention by individuals embarking on neuropsychological investigation.

On this basis, *Studies in Neuropsychology* ranks as a volume of consequence for contemporary students of the complex interplay between the brain and mental function. Benton's work covered a broad range, including cerebral localization; hemispheric dominance; problems in developmental neuropsychology such as dyslexia and mental retardation; aphasia, dementia, and other neuropsychological problems of the aged; and a number of specific areas such as constructional and spatial disorders, reaction time studies, the use of double simultaneous stimulation in neuropsychological research, and an interesting series of papers on the Gerstmann syndrome. *Studies in Neuropsychology* can be recommended as pleasant and valuable reading for any contemporary neuropsychologist and for neurologists, psychiatrists, psychologists, linguists, philosophers, educators, and others interested in brain function.

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Neuropsychological Assessment of Neuropsychiatric Disorders, *edited by Igor Grant, M.D., F.R.C.P.(C), and Kenneth M. Adams, Ph.D., A.B.P.P. New York, Oxford University Press, 1986, 497 pp., $45.00.*

The rapid development of neuropsychology in the past decade has created a void in the availability of authoritative and comprehensive textbooks that can provide introductory overviews of the field for students and professionals in related disciplines. Until quite recently, individual journal articles and workshops were the only avenue for acquiring such background. Although several textbooks and handbooks of neuropsychology have been offered in the past few years, these have been of varying scope and quality. Assembling a textbook for a field that is in mid-flight and has yet to benefit from a perspective afforded by tradition is a challenge. *Neuropsychological Assessment of Neuropsychiatric Disorders* is an ambitious and important attempt to fill this void. Dr. Grant, a prominent neuropsychiatrist, and Dr. Adams, a leading neuropsychologist, have assembled an impressive set of contributors for the volume.

The text is divided into two sections. Chapters in the first section, comprising one-fifth of the book, provide brief introductions to three models of assessment and discussions of qualitative test analysis and computer applications. The remainder of the book is devoted to chapters reviewing recent research in a wide range of neurological, psychiatric, and general medical disorders.

The first topical area, assessment methods, could easily be the subject of an entire volume, as it is in *Clinical Applications of Neuropsychological Test Batteries* (1). The dimensions along which assessment approaches have been divided include empirically derived versus theoretically based test batteries, relative emphasis on quantitative versus qualitative analysis, and fixed versus flexible batteries of tests. The book gives a glimpse of some of these approaches.

Chapter 1, by Ralph Reitan, reviews the historical development of the Halstead-Reitan Battery, a fixed battery method that is empirically based and primarily subjected to quantitative analysis. Reitan briefly covers the component tests of the Halstead-Reitan Battery, the logic of interpretation, and some of the many validity studies. A detailed bibliography covers much of the initial research using the Halstead-Reitan Battery.

Chapter 2, by McKenna and Warrington, introduces the "analytical approach," a school of neuropsychology heavily weighted toward cognitive psychology, which the authors claim "overcomes the very real barrier posed by notions of equipotentiality." This model is primarily theory driven and aims to fractionate neurologically relevant psychological processes into discrete skills. New tests are developed to assess these discrete functions and their subcomponents.

In chapter 3 Goldberg and Costa present an example of qualitative analysis in neuropsychology, building on the work of Alexander Luria, the late Russian neuropsychologist. The authors argue that "most meaningful quantification in neuropsychology occurs only after sufficient observation and theory building." Continuing in this vein, Milberg, Hebben, and Kaplan describe in chapter 4 the "Boston process approach" developed by Edith Kaplan, which emphasizes qualitative analysis of test behavior rather than the final score obtained by a patient. The Boston method is to administer a core battery of tests and then add "satellite" tests to assess specific functions or hypotheses about the patient in greater detail. Thus it has also come to be known as the "flexible battery" or "hypothesis-testing" approach.

Chapters 5 and 6, by the editors and their colleagues, deal with issues currently receiving considerable attention: possibilities for computerization of various aspects of neuropsychological assessment and subject variables (age, education, and sex) that influence the interpretation of test results.

Chapters 7 through 13 are concerned with more traditional psychiatric disorders and treatment. In chapter 7 Yozawitz reminds us of the historical role of neuropsychology in psychiatry—the classification of patients as having neurological versus psychiatric disorders. It has become clear that many psychiatric patients without otherwise detectable neurological diseases show impaired performance on neuropsychological test batteries, contributing to the renewed emphasis on biological bases for many psychiatric disorders. Yozawitz, who has been involved in cognitive rehabilitation with psychiatric patients, proposes a model for a contemporary reintegration of neuropsychological evaluation and rehabilitation services into psychiatric settings.

Chapter 8, "The Neuropsychology of Schizophrenia" by Goldstein, provides an overview of major issues in the development of a neuropsychological perspective on this disorder. The overview is balanced and informative although, curiously, in its discussion of Crow's typology of type I and type II schizophrenias (2) it confuses type I and type II (p. 164).

In chapter 9 Kaszniak covers the "Neuropsychology of Dementia," an area that has received extensive attention in recent years. In addition to issues in the psychometric assessment of the elderly patient, Kaszniak briefly reviews clinical features, pathology, rating scales, laboratory studies, and epidemiology.

In chapter 10 Caine deals with the "Neuropsychology of Depression" and the manifestation of depression as pseudodementia. Although it is a good overview, this chapter neglects the laterality hypothesis in affective disorder, which, even if controversial, is one of very few that link brain function to depression. This chapter's focus on pseudodementia appears a bit narrow for the mission of the volume.

Chapter 11, by Rourke and colleagues, presents several case studies and a conceptual framework for addressing deficits in adults who had learning disabilities as children. In chapter 12 Squire provides an excellent discussion of issues in the assessment of memory processes. He includes specific test recommendations and reprints the Self-Rating Scale for Memory, which his group has used in studies of ECT. Joschko, in chapter 13, reviews neuropsychological studies of psychosurgery.

Chapters 14 through 20 provide similar reviews of the status of current clinical research on other diseases that can affect higher cortical function. These include epilepsy (by Trimble and Thompson), closed head injury (by Bond), Parkinson's disease (by Passafiume, Boller, and Keefe), cerebrovascular disease (by Brown, Baird, and Shatz), alcoholism (by Loberg and by Brandt and Butters), and drug abuse (by Carlin). As can be expected from contributions by active researchers, there is a tendency to emphasize the authors' own research. However, these chapters are well written and provide a good overview of the respective areas.

Overall, *Neuropsychological Assessment of Neuropsychiatric Disorders* provides a useful reference for practicing clinicians in psychiatry, neurology, and neuropsychology. Chapters dealing with methods of assessment will be helpful to beginning students in neuropsychology and to professionals in related disciplines who require an introduction to the topic. Chapters focusing on psychometric issues may be of more specific interest to neuropsychologists.

The authors "make no pretense of completely covering the many important approaches that exist." They did ignore two neuropsychological test batteries that have had a major impact on the field. Missing is the pioneering and highly influential set of procedures developed by Arthur Benton and colleagues (3), which have been used extensively in the evaluation of aphasia and right hemisphere damage. Likewise, the Luria-Nebraska Battery, although generating considerable controversy, is being widely used.

Although in their preface the editors emphasize the recent trend toward an interface between neuropsychology and various medical specialists, including "pulmonary physicians, diabetologists, nephrologists, cardiologists, oncologists, and specialists in infectious diseases," there are no chapters specifically devoted to an exploration of this interface. Instead, the text primarily focuses on traditional neurological and psychiatric disorders. Furthermore, another dimension of interdisciplinary collaboration that increasingly contributes to advances in neuropsychology is integration of behavioral data with neuroimaging studies of regional brain anatomy and physiology. The contribution of this volume could have been enhanced by inclusion of work in this area.

Other than the brief preface and some cross-referencing of chapters, there is no systematic attempt to provide an overall perspective or integration. Although most chapters are excellent and certainly stand on their own, more synthesis would have been desirable for students, particularly with regard to assessment approaches. Similarly, in the section on neuropsychiatric disorders, an integrative chapter might have dealt with issues such as the hypothesized neurochemical relationship between Parkinson's disease and schizophrenia. On the other hand, the book is thoroughly indexed by author, subject, and test and the chapters taken together provide an excellent bibliography. One of us (A.J.S.) has used the book twice in a graduate course in neuropsychological assessment and encountered positive responses from students. Notwithstanding its minor flaws, *Neuropsychological Assessment of Neuropsychiatric Disorders* fills a need and is likely to become a standard reference.

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Aspects of Epilepsy and Psychiatry, *edited by Michael R. Trimble and Tom G. Bolwig. New York, John Wiley & Sons, 1985, 256 pp., $42.00.*

The excitement and promise of basic research in the neurosciences have captured the behavioral sciences. As psychiatry moves into this increasingly high-tech and promising area of research it is important to note that explorations of dysfunctions of the CNS can also occur in the clinical setting. This excellent monograph on psychiatry and epilepsy highlights the clinical, theoretical, and research potential of the examination of the behavioral aspects of a neurological disorder. This is not a new area of research for psychiatry and in fact represents the close traditional collaboration between psychiatrists and neurologists from the time that they were one specialty. The contributors to this monograph are an international group of well-known investigators, e.g., Robert Post, Ted Reynolds, Eric Sindrup, Janice Stevens, and Michael Trimble. The book covers the behavioral aspects of epilepsy quite well. The first chapters of the book delineate the overall types of psychiatric disturbances seen in patients with epilepsy and then goes on to more discrete behaviors often associated with seizure disorders such as aggression, depression, and altered sexual behavior. Other chapters deal individually with the possible etiologies of these behavior disturbances in seizure disorders by reviewing recent positron emission tomography (PET) findings as well as some very interesting neuropathological and electrophysiologic studies of these patients. There are several excellent chapters on the use of anticonvulsant medication in seizure disorder patients and in psychiatric patients without seizure disorders.

This book presents well the controversies abounding in this area. For example, are the psychotic phenomena of seizure disorders related specifically to the temporal lobe or are the psychotic phenomena also apparent with more generalized seizure disorders? Is there an increase in violence and aggression in patients with seizure disorders? Is there a change in their sexual behavior? Are they more religious and philosophical? Although there are some data to support yes or no answers to most of these questions, it is clear that certainty has not yet been achieved. However, the possibility that specific behaviors (violence, psychosis, changes in sexual behavior, philosophical concerns, etc.) can be related even inconsistently to specific disorders or lesions is intriguing and may illuminate aspects of psychopathology in the future.

For the clinician there is an excellent chapter by Reynolds on the use of anticonvulsant drugs and a comprehensive review by Post and Uhde on the use of anticonvulsants in nonepileptic psychosis. I am sure that few clinicians know that carbamazepine has some effect on hormones that could affect sexual function. There is a marked difference in the effects of carbamazepine, phenytoin, and, to some extent, valproic acid on cognitive functions. However, these effects on memory and concentration are also related to blood levels, to the particular drug, and the number of drugs (there are fewer cognitive changes when only one drug is used). With the increasing use of anticonvulsants in psychiatry, clinicians should be knowledgeable about such potentials.

There is also a very thought-provoking chapter by Robertson on depressive symptoms in seizure disorders. The substantial number of depressive symptoms he cites that are associated with seizure disorders (unrelated to a psychological reaction to the seizure disorders) is remarkable and certainly deserves further study.

The theoretical questions abound. Post very clearly cites evidence demonstrating the effectiveness of anticonvulsants in bipolar disorders and notes the different pharmacological profile of the anticonvulsants. Although the vast majority of patients with major psychiatric disorders do not have seizure disorders, it is of interest that there is this overlap of patients who respond both to anticonvulsants and to more traditional psychiatric medications. Further, it is intriguing that the effectiveness of carbamazepine is mainly for manic episodes and prophylaxis; unlike lithium, it does not seem to be effective for the depressive phase of the illness.

The investigator reading this monograph will come up with many ideas for further study. The clinician will find many insights into behavior and many practical applications—e.g., differential diagnosis and the use of anticonvulsants. The student should find the whole topic intriguing because it truly brings together the mind and the body in a most exciting manner. This book is highly recommended.

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Psychopathology in Epilepsy: Social Dimensions, *edited by Steven Whitman and Bruce P. Hermann. New York, Oxford University Press, 1986, 302 pp., $39.95.*

There has been a plethora of books on epilepsy, many of them multiauthored books emerging from conferences. A criticism of much of this literature is that the social aspects of epilepsy have been less explored and written about than the medical aspects. In recent years, a considerable amount of work has been done on the biochemistry of epilepsy and new anticonvulsant drugs. This book, however, is timely and concentrates on just those aspects of epilepsy which have been ignored and which are so important for an understanding of the condition and its management.

In their preface the editors rightly point out that the modern era of investigation with regard to the psychopathology of epilepsy began in the late 1940s, when Gibbs and colleagues suggested that patients with temporal lobe epilepsy were especially susceptible to developing psychopathology, particularly psychosis, because their limbic systems functioned abnormally. The editors also point out that in spite of a considerable amount of research there is continuing disagreement as to the role of neurological as opposed to psychosocial factors in the ultimate development of psychopathology in epileptic patients.

The book is divided into four sections. In the first, Setting a Perspective, the editors provide an overview of the problem and suggest a multifactorial model to explain psychopathology in epilepsy. This model encompasses neurological, psychosocial, and medication variables.

Section two examines the social dimensions of epilepsy in relation to psychopathology, beginning with an interesting chapter on doctors, information, and the control of epilepsy. It seems that many patients complain of the quality and quantity of information they receive from physicians, and, as with many other chronic medical conditions, the suggestion is made that providing patients with more information would give them more control over their illness and therefore their lives. Other chapters deal with the fear of actually having seizures, the perceived social consequences of epilepsy, and perceptions of control among children with epilepsy.

Section three deals with stigma and epilepsy. Particular emphasis is given to children and the way those with epilepsy are viewed by their peers and educators. The fourth and final section of the book deals with psychosis and violence in epilepsy.

This book can be recommended to those who have an interest in epilepsy as a problem beyond seizures, and it contains some useful reviews and some research data in an area that has led to little investigation until recently. It will also be of interest to psychiatrists who wish to introduce themselves to some of the psychosocial aspects of epilepsy. In general the book serves to emphasize the importance of extending the links between psychiatry and epilepsy, as has been happening in recent years.

Psychiatrists who are concerned with the concept of chronic disease and stigma will be interested to read the following on page 190:

> In a 1974 article in *Nursing* magazine, Loy Wyley referred to an unreferenced study that reported that society rejected people with epilepsy at a higher rate than it rejected the mentally ill. There is a great irony here. Society stigmatizes people with epilepsy in part because it perceives them to be mentally ill, and at the same time it is less prejudiced against persons who are mentally ill. An interesting sidelight to this irony was the exchange between the Epilepsy Foundation of America (EFA) and an advocacy organisation for mental retardation. The EFA has produced educational information that states that having epilepsy is not the same as being mentally retarded. The other organisation has responded by asking how the EFA would feel if the former ran an announcement saying that "most mentally retarded people don't have epilepsy."

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CLINICAL ASSESSMENT AND LABORATORY TESTS

Diagnostic and Laboratory Testing in Psychiatry, *edited by Mark S. Gold, M.D., and A.L.C. Pottash, M.D. New York, Plenum, 1985, 270 pp., $32.50.*

As a consequence of the impressive developments in biological psychiatry and clinical psychopharmacology over the last decade, interest has grown in diagnostic procedures and laboratory testing for the evaluation and treatment of psychiatric disorders. Unfortunately, however, the attitude of psychiatrists to such procedures and testing is far from unanimous. In fact, Drs. Gold and Pottash stress in the preface to this book that

> some psychiatrists do not draw blood and do not have a working understanding of the laboratory and the procedures available and as a result do not order laboratory testing. . . . Although they themselves do not order tests, these psychiatrists have the illusion that their patients are being properly evaluated or "cleared" for psychiatric treatment. Nothing, in our experience, could be further from reality than this notion, which is shared by all too many nonmedical psychotherapists and a small number of psychiatrists.

The editors describe the scope of this volume as the "description of the major diagnostic procedures and emphasis on the 'how to's' (how to use, how to interpret, how to choose which patient will benefit)." The book includes 19 chapters, and the editors contribute to most of them, which provides a good degree of cohesion.

The initial chapters are "Medical Evaluation of the Psychiatric Patient" by T.W. Estroff and M.S. Gold. "Neurological Evaluation of the Psychiatric Patient" by D.A. Gross and M.S. Gold, "Tests of the Hypothalamic-Pituitary-Adrenal Axis" by M.S. Gold and M.H. Kronig, "Thyroid Testing in Psychiatric Patients" by M.H. Kronig and M.S. Gold, and "Other Neuroendocrine Tests" by H.R. Pearsall and M.S. Gold. These are followed by a review of neurochemical tests by M.S. Gold and M.H. Kronig in a chapter entitled "Norepinephrine and Serotonin Tests."

Particularly exhaustive is the chapter "Therapeutic Drug Level Monitoring in Psychiatry" by S.H. Preskorn, M.S. Gold, and I. Extein. This fully referenced chapter clearly explains the clinical and toxicological implications of monitoring the drugs given to psychiatric patients in therapy. Unfortunately, however, the chapter focuses on antidepressants, lithium, and anticonvulsants and does not mention the antipsychotic drugs.

"Evaluation of Anxiety Disorders" by C.L. Hamlin and A.L.C. Pottash is an especially useful and up-to-date chapter. These authors discuss the evidence for a dichotomy between exogenous and endogenous anxiety.

Other topics dealt with in this volume include "Platelet and Trait Markers" by M.S. Gold and H.R. Pearsall, "Central Nervous System Neurodiagnostic Devices" by W. Hapworth, "Nutritional Deficiency Syndromes in Clinical Psychiatry" by F.C. Goggans and M.S. Gold, "The Use of Psychiatric Rating Scales in Clinical Evaluation and Treatment" by R.M. Allen and M.S. Gold, "Drug Abuse: Interpretation of Laboratory Tests" by K. Verebey, D. Martin, and M.S. Gold, "Evaluation of Affective Syndromes" by I. Extein, M.S. Gold, and F.C. Goggans, "Evaluation of Psychotic Syndromes" by D.E. Sternberg and A.L.C. Pottash, "Evaluation of the Substance Abuser" by L. DeMilio, M.S. Gold, and D. Martin, and "The Assessment of Anorexia and Bulimia" by W.S. Rea and M.S. Gold.

"The Clinical and Laboratory Evaluation of Dementia" by R.M. Allen and M.S. Gold critically reviews the literature on biological markers of the main psychiatric disorders, their diagnostic assessment, the rating scales and neuroradiological tools involved, and the rationalization of treatments.

It seems to me that this book fails to emphasize the poor sensitivity or specificity of some of the tests described. Overall, it does not stress the differences between laboratory testing in internal medicine and in psychiatry. In psychiatry, some studies finding high confidence and specificity for some diagnostic markers have not been confirmed by further studies.

In summary, this book offers valuable and up-to-date help for psychiatrists, neurologists, and clinical psychopharmacologists for managing clinical testing procedures in psychiatry.

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The Psychiatric Evaluation in Clinical Practice, *by Roger A. MacKinnon, M.D., and Stuart C. Yudofsky, M.D. Philadelphia, J.B. Lippincott Co., 1986, 277 pp., $24.50.*

Given the diversity, activity, and rapid advances in our field, no contribution could be more laudable than a work that updates and integrates the clinical evaluation of psychiatric patients. Brilliant in its concept and timing but uneven in its execution, *The Psychiatric Evaluation in Clinical Practice* will help clinicians and trainees to achieve this integration. No single school of thought owns exclusive rights to the psychiatric evaluation; it is as much biological as psychological, as much descriptive as inferential (psychodynamic). Accordingly, this text consists of six chapters, each presenting a different facet of the psychiatric examination. The authors proffer a multifaceted view of the psychiatric evaluation, and the reader, as if viewing in turn the six symmetrical sides of a cube, hopes, like Plato, to discern beneath the chaos of clinical material an eternal form or formula.

Chapter 1, "The Psychiatric Interview," discusses how to conduct oneself during the interview, how to develop rapport with the patient, and how to understand transference and countertransference as they appear in the initial interview. Chapter 2, "The Clinical Examination of the Patient," develops an in-depth format for data gathering and presents outlines for the written psychiatric history and mental status examination. Chapter 3, "Biological Testing in Psychiatry," offers a cogent and evenhanded discussion of the current status of neuroendocrine assays, electrodiagnostic and brain imaging techniques, and measurement of serum levels of psychotropic medications in psychiatric diagnosis and treatment. Chapter 4, "Evaluation of Regional Cortical Functioning," briefly reviews cortical localization and the assessment of dementia, pseudodementia, and delirium. Chapter 5, "Psychological Testing and Psychiatric Rating Scales," is a listing of assorted rating scales and brief basic descriptions of the WAIS-R, the Rorschach, the Thematic Apperception Test (TAT), the MMPI, and a few other test batteries. A lengthy appendix to this chapter—which is visually hard to follow—reproduces and describes seven commonly used psychiatric rating scales. The final chapter, "DSM-III Diagnosis and the Psychodynamic Case Formulation," consists of a concatenation of two discrete topics. The first section of this chapter explains at a painfully rudimentary level the *DSM* multiaxial diagnostic system and quotes extensively from *DSM-III* itself.

The second section comprises a review of ego functions and Freud's structural model of the mind. It also presents a format for developing a psychodynamic case formulation. An appendix to this chapter presents three comprehensive examples of written psychodynamic case formulations. Each chapter lists dozens of books and articles as suggestions for further readings.

The individual chapters vary widely in their execution. As a fourth-year resident in psychiatry, I found the section on the written psychodynamic case formulation to be of tremendous assistance in preparing my own case reports. The chapter on the psychiatric history and the mental status examination allows the authors to demonstrate their vast experience as clinicians. They are not content to merely develop an outline for data gathering but also offer practical information and examples as to what sorts of data are and are not clinically meaningful to the overall understanding of the patient. The nadir of the book is the very weak chapter on psychological testing and rating scales, which is little more than an assemblage of available tests and fails to address the questions of what tests to use for which patients under what circumstances. At one point in this tedious chapter, the Global Assessment Scale (1) is reprinted in its entirety, followed immediately by a section purporting to explain how to interpret the results, which is a verbatim duplication of the scale itself in a different typeface. Furthermore, those who are familiar with *The Psychiatric Interview in Clinical Practice* by MacKinnon and Michels (2) will experience an eerie sense of déjà vu while perusing chapter 1, which is largely a rehash of that classic text.

Overall, this is a work so timely and well conceived, addressing a topic so central to our field, that despite its flaws in execution it should be examined by all psychiatric residents and any subspecialist who would like to broaden his or her perspective on the contemporary evaluation process. The reader of this volume will be rewarded not with the discovery of a Platonic ideal but, instead, with a Heraclitean admonition that the only thing which is constant is change itself. This book reminds us that the psychiatric evaluation will be ever changing and growing in direct proportion to the changing methods and concepts of psychiatry itself.

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PSYCHOPATHOLOGY

Essential Psychopathology, *by Jerrold S. Maxmen. New York, W.W. Norton & Co., 1985, 381 pp., $29.95.*

Were the Old Testament's Ecclesiastes reincarnated as a contemporary psychiatrist, he would doubtless record that of making many books—in particular, many turgid, unenlightening, and downright bad psychiatric books—there is still no end. All the more surprising and wonderful, then, to discover Jerrold Maxmen's vigorous, lucid prose in this introductory text on diagnostic psychopathology. Maxmen's case histories, for example, describe living, breathing people; instead of the all too common style of "This 58-year-old woman developed a depressed mood, insomnia, suicidal thoughts . . . ," he grabs us immediately with, "At 58, Amy's life stopped." He has clear opinions, forcefully expressed: "Any clinician who evaluates a patient's condition solely in terms of whether it meets *DSM-III* criteria is a jerk. (The jerk would also be misapplying *DSM-III* and misunderstanding diagnosis.)" Here's an author who knows how to get the reader's attention and keep it.

To complement its engaging style, the book has clear organization. Maxmen begins by describing introductory concepts of psychopathology (using *DSM-III* as a framework), then provides general chapters on assessment, diagnosis and prognosis, etiology, and treatment. This section ends with a clever "sample case history" of Sherlock Holmes's cocaine addiction. Succeeding chapters cover the major groups of mental disorders in the format of clinical presentation, epidemiology, etiology and pathogenesis, differential diagnosis, and (briefly) management and treatment. Appendixes contain the *DSM-III* classification outline, a "medical-psychiatric history form," a symptom glossary, psychiatric medication doses and side effects, and the *DSM-III* axis V codes (called "problems in living"). All the main chapters are full of effective summaries of available empirical data, laced with wit, sensible comments, and plausible hypotheses where data are lacking. The student will learn much and learn it enjoyably.

There are a few flaws. It seems curious that the publishers did not wait a year so that the book could be synchronized with *DSM-III-R*, despite Maxmen's disclaimer that "few of the changes in *DSM-III-R* will be major" (certainly debatable now). The assessment chapter labels the physical examination as "auxiliary data" and tells the student nothing about a psychiatrically focused physical examination. Maxmen notes that asking about violent and homicidal tendencies is commonly neglected in the initial history, but then he neglects them himself. Laboratory tests are relegated to an unexplicated table that lists "parathyroid tests" (besides serum calcium) as routine psychiatric screening tests. In contrast to the laudable insistence on validated empirical data in the rest of the text, the section on the mental status examination repeats several traditional tests of low diagnostic validity and neglects more recent and better validated clinical batteries. There are occasional debatable statements (e.g., that schizoid personality disorder and schizophrenia "are unrelated," when the data are actually controversial or unavailable) and a few factual errors (e.g., that Korsakoff's psychosis is a "permanent dementia," whereas it's actually an amnestic disorder and sometimes reversible). For the next edition, the author might expand the somewhat rushed etiology chapter and drop the detailed appendix on psychiatric medication side effects, since these medications really are not covered in depth anywhere else in the text. But these shortcomings do not seriously compromise the book's generally high standard.

Physical characteristics of the book are also well done: durable binding, attractive typography, pleasing layout, and few typographical errors (although thioridazine is misspelled six times in appendix E). The index is adequate, and the price is reasonable for the value obtained. For medical students' learning, nonpsychiatric physicians' reviewing, or just a plain good read, this is a winner.

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Contemporary Directions in Psychopathology: Toward the DSM-IV, *edited by Theodore Millon and Gerald L. Klerman. New York, Guilford Press, 1985, 712 pp., $50.00.*

The diagnostic classification of mental disorders remains a controversial and much debated process. In decades past, dissatisfaction with psychiatric classification revolved around the lack of reliability of psychiatric diagnosis, its association with unproven theories, and the negative consequences of assigning labels. These concerns and the influences of biological psychiatry stimulated work that resulted in a margin of improvement and the publication of *DSM-III*. Despite intensive and productive efforts to form a clinically sound and valid classificatory system, there is still much work to be done.

It therefore becomes obvious that the major thrust in solving a problem of this magnitude should be in the direction of reliance on scientific research and validation. What steps can be taken in this direction? Tapping the expertise of distinguished and promising investigators in the field is one obvious measure. A second is to examine the strengths and weaknesses of the current classification system. Next, a comprehensive analysis of the conceptual issues and methodologies in psychopathological research is a likely prelude to assessing new research findings regarding specific mental disorders. This volume addresses these objectives and identifies issues and methods for improving the scientific quality of future classifications. The editors and 3[illegible] authors have combined their resources to review the literature of the emerging science of psychopathology, adding to it their own investigations and suggestions for improving on the current psychiatric classification. The editors, Drs. Millon and Klerman, are acknowledged authorities on psychopathology who contributed to the development of *DSM-III* and its revision, *DSM-III-R*. Recognizing the diversity of opinion in this field, the editors allowed the distinguished contributors from a variety of professions to be original, to state their opinions, and to disagree with each other and, at times, the editors. As might be expected, there is some redundancy, and many authors address the same problems, albeit through dissimilar approaches.

The book has five sections, beginning with one by the editors on the historical background of contemporary psychopathology. Relying on their personal experiences, Drs. Millon and Klerman provide an interesting introduction that affords the reader insight into the influential process which resulted in *DSM-III*. The next section deals with classification and *DSM-III*. Here Dr. Eysenck echoes many of his suggestions from previous publications while leveling a solid critique at *DSM-III*. The contributors who follow him delineate the accomplishments, shortcomings, alternatives, and consequences of *DSM-III*.

The editors devote six chapters to conceptual issues. Drs. Grunbaum, Meehl, Cantor and Genero, Strauss, Scheff, and Corning analyze a wide variety of theoretical and practical points. These chapters are well written and of high academic caliber. The brief fourth section, on methodological schemes, should prove valuable to mental health professionals confronted with the arduous task of deciphering the approaches and methods used in psychopathological research. Harvey Skinner presents a construct validation approach that "can play a vital role in upgrading the scientific quality of classification research." Dr. Lorr proposes the synthesis of categorical and dimensional models for classifying patients with psychosis, and Drs. Frances and Widiger call for a dimensional system for the classification of personality disorders. Other authors demonstrate how statistical analysis can be used to evaluate categories and how little is understood about the taxonomic structure of psychiatric classification.

The final section focuses on proposals for *DSM-IV* syndromes. One of the attractions of this section is that it stems directly from the authors' clinical and research experiences. Syndromes covered include attention deficit disorder, depression, the bipolar spectrum, and schizophrenia. The final five chapters focus on personality disorders.

One criticism I have of this book is the lack of a general summation. This is not a trivial work; many chapters require rereading for adequate comprehension. A distillation of the salient points of the volume would have added clarity and brought together precise measures for future deliberations. There is a wealth of material available for the serious scholar in this extensive volume, but it is uneven in quality and content as well as in writing style.

Given the recent publication of *DSM-III-R*, the timeliness and relevance of *Contemporary Directions in Psychopathology: Toward the DSM-IV* are apparent. Furthermore, I consider this book required reading for all those involved in developing *DSM-IV* and the mental disorder chapter of

ICD-10. In short, this excellent book should do exactly what its subtitle suggests—guide psychiatry toward a more valid *DSM-IV.*

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SPECIFIC DISORDERS

Fears, Phobias, and Rituals: Panic, Anxiety and Their Disorders, *by Isaac M. Marks, M.D., F.R.C.Psych. New York, Oxford University Press, 1987, 641 pp., $42.50.*

This encyclopedic volume is a reviewer's nightmare. It is written by one of the eminent researchers and clinicians in the anxiety disorders and is a summation of the field. Furthermore, it contains several distinguished chapters designed to place normal fear in an evolutionary context. How does one proceed to cover the depth as well as breadth of this highly detailed effort?

Perhaps Dr. Marks might provide some avenue of exposure to allow the fearful reviewer and reader to become desensitized to its massive structure. The table of contents offers an overview of the book's four parts. Part one, Normal Fear, includes chapters on fear, defense, and evolution; fear-evoking situations; and fear behaviors. The fear strategies described include withdrawal, immobility, aggressive defense, deflection of attack, and submission. Part two, Mechanism, includes chapters on the development of fear, the genetics of fear, the physiology of fear, and the learning of fear. Part three, Clinical Syndromes, includes chapters on the classification, prevalence, and relationship to other problems of phobic and obsessive-compulsive phenomena; the agoraphobic syndrome; social and specific phobias; traumatic phobias; illness phobias; children's phobias; and obsessive-compulsive disorder. Part four, Treatment, includes chapters on psychological and physical treatment. At the end of each chapter the author provides succinct summaries for preview as well as for review. In view of all this, perhaps it might not be too difficult to master this book.

The first chapter provides a set of definitions for the intrepid explorer of this terrain: "Fear is the usually unpleasant feeling that arises as a normal response to realistic danger. Anxiety is an emotion similar to fear but arising without any objective source of danger" (p. 5). But then Dr. Marks states that "panic denotes a sudden upsurge of acute, intense fear, often associated with frantic attempts to escape." Since fear is associated with a response to realistic danger, would not the term "intense anxiety" be more correct than "intense fear" here?

Across species, fear behavior removes, protects, or defends the animal from present or anticipated threat (p. 9). With this operational definition Dr. Marks proceeds to present several fascinating descriptions from animal research that demonstrate what frightens animals and how they respond to being frightened. The manner in which eyespots on certain moths and staring in primates work to incite fear is quite interesting, as are the many ways in which animals defend themselves. Particularly interesting is that freezing (or playing possum, playing dead) fools certain predators who would not attack anything unless it was moving. Some animals defend themselves by assuming the visual appearance of some deadly member of their own species, thus forcing predators to avoid them despite their inability to deliver a lethal blow. As suggested by these examples, this part of the book is intended only for wide-ranging clinicians or ethologists and experimental psychologists.

The courageous reader may begin to lose a little heart in the chapter on the development of fear. One must be compelled to consider the possibility that many simple phobias like stranger anxiety, fear of fire, and fear of snakes are phylogenetic holdovers through which children pass during their ontogeny. They should be more frightened of cars and the frayed ends of an electrical cord. And we should be more frightened of nuclear war than of our home team's losing to some visiting foe. But the chapter is loaded with data and references to research, and this stimulus overload does not abate for the remainder of the book. There is no easy exposure now, just the hard work of plodding through information that yields only a few reliable conclusions.

For the researcher interested in background reviews of specific content areas, this detail is rich and labor saving. For example, for someone writing a paper on the relationship between anxiety and depression, Dr. Marks succinctly provides a scholarly review that critically evaluates existing findings. One other advantage in addition to his erudite comments is the fact that many of his references go back past 1980, the limit of many computer reference searches.

The author is a passionate advocate of exposure therapy for the anxiety disorders. He believes that medications are interim and impermanent treatments and backs up his assertion with much evidence. The psychiatric clinician entrenched in pharmacotherapeutic treatments will need to pay attention to these data. If one wishes to avoid going through this volume to achieve these ends, Dr. Marks has written two articles (1, 2) that provide easier access for clinicians to his treatment approaches.

What could be missing from this book? I was fascinated to note Dr. Marks's plan to omit spontaneous panic from general emphasis (p. viii). One reason appears to be his belief that panic attacks without agoraphobia are not nearly so disabling as panic attacks which lead to agoraphobia (p. 289). Our work with panic disorder in cardiology populations suggests that panic attacks alone are quite disabling (3).

Marks makes many different interesting points throughout the book. On pages 224–227 he and a colleague attempt an integration of the findings from neurophysiology to define the brain mechanisms responsible for fear behavior. They suggest that escape is partly mediated by circuits through the peri-aqueductal gray matter, some hypothalamic nuclei, and the amygdala. Tonic immobility is affected by the median raphe nuclei in the brainstem and is likely to be mediated across phyla by serotonin. They ask whether obsessive-compulsive disorder could originate in the failure of a normal "checking" function of a comparator in the septomarginal system. Are spontaneous panics massed discharges of central noradrenergic neurons in the locus ceruleus? Since both antidepressants and repeated stress lead to widespread down-regulation of central noradrenergic postsynaptic receptors, could it be that both drugs and exposure work on the same receptors?

Dr. Marks notes that learning resembles genetic transmission and that its medium is culture, which is Lamarckian in the sense that acquired cultural characteristics can be transferred to new generations (p. 229). He destroys behavioral psychology's dependency on Little Albert (Watson and Rayner's paradigm for conditioning) and opens the way to melding genes and environment (pp. 231–232). He attempts to define courage (p. 275).

This book is a towering addition to our comprehension of the anxiety disorders. It is primarily a reference text for persons interested in extending their grasp of the anxiety disorders. It is difficult, ponderous reading and requires some anxiety to propel one through it.

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A Clinical Guide to Alcohol and Drug Problems, *by Joseph Westermeyer. New York, Praeger, 1985, 325 pp., $33.85.*

The goal of Dr. Westermeyer's book is to be a clinical guide for physicians, particularly the generalists who inevitably encounter patients with alcohol and drug problems. He fulfills his goal admirably in regard to alcohol, but because of the multiple nature of drug problems, he is able only to scan this aspect. This is especially marked in relation to his very thorough and considerate handling of the alcohol issues.

Despite the above caution, this volume presents the scope and range of the issues associated with alcohol and other substance use and abuse. The format of the volume is quite useful for the clinician who may wish to read it and then use it as a reference. It certainly allows the clinician to understand the principals of diagnosis of substance abuse problems, the types of clinical management, and the possible range of treatments and rehabilitative opportunities that might be available within a given community. Dr. Westermeyer gives a clear and succinct recitation of all of these areas.

The volume gives the beginnings of an appreciation to the generalist of the complexity of a field that is coming into its own in this era of subspecialization. Reading this book should allow the generalist to feel more comfortable in understanding the issues that are involved in dealing with substance-abusing patients, in making the diagnosis, and in directing patients to the appropriate form of treatment or rehabilitation. I feel that this book is a valuable addition to the armamentarium of the general medical practitioner or the general psychiatrist in dealing with these disorders.

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Coping With Life Crises: An Integrated Approach, *edited by Rudolph H. Moos in collaboration with Jeanne A. Schaefer. New York, Plenum, 1985, 424 pp., $45.00.*

The preface of this useful book notes that it focuses on "new developments" in the area of human competence and coping behavior and that it considers the interplay between environmental contexts and personal resources and their impact on how individuals cope with life transitions and crises.

The 29 chapters are organized into 11 sections. The first seven sections focus on normative life transitions such as early childhood, adolescence, career choice, parenthood, divorce, remarriage, middle age, retirement, death, and bereavement. It begins with a conceptual overview of life transitions and crises written by Moos and Schaefer. The next four sections focus on coping with "unusual crises" such as alcoholism, migration, natural and manmade disasters, violence, terrorism, war, and imprisonment.

What is remarkable about this book is neither the array of topics nor the way they are organized but the list of internationally known scholars who contributed to it: Ann Burgess, Paul Chodoff, Robert Jay Lifton, Frank Ochberg, Beverly Raphael, Carlos Sluzki, Lenore Terr, Judith Wallerstein, and Robert Weiss, to name a few. Unfortunately, only the first chapter is original. All others are reprints from other publications, mostly scholarly journals (e.g., *Harvard Business Review, Family Relations,* and the *Journal of Adolescent Health Care*), published as far back as 1976.

Moos and Schaefer's initial overview chapter is an ambitious attempt to provide a historical overview of the study of life crises, crisis theory, their own conceptual framework, and prevention, intervention, and treatment. It provides a good summary of the outstanding research findings of Professor Moos that have emerged over the years.

The claim that this anthology represents recent developments is somewhat misleading, since few of these papers were recently published. Moreover, as an anthology of reprinted works the style of writing and chapter structure is highly variable. It is notable that although Jeanne Schaefer compiled, organized, and coauthored the most important contributions of this collection (the overview chapter and each of the introductions to the sections), she was not credited with coeditorship.

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Understanding and Treating the Psychopath, *by Dennis M. Doren. New York, John Wiley & Sons, 1987, 268 pp., $32.00.*

This book and its author represent somewhat of an anomaly in recent work on antisocial personality disorders. First, instead of using *DSM-III* or *DSM-III-R* definitions of antisocial personality Doren works with the older concept of psychopathy. Second, he is in a small minority in feeling that behavioral gains can be achieved through psychotherapy with antisocial psychopathic individuals.

This book is divided into two major sections. The first deals with theories of sociopathy and the second deals with practical items of therapy. In the theoretical section Doren examines four different theories of sociopathy: Gough's theory (the psychopath as deficient in role playing abilities), Eysenck's theory (the psychopath as a genetically predisposed deficient learner), Quay's theory (the psychopath as a pathological stimulation seeker), and Hare's theory (psychopathy as biologically based). Doren tests each of these theories against the six criteria of a "good" theory specified by Hall and Lindzey (1). Doren's analysis is reasonable and readable.

At the end of this section he proposes his own integrative theory of psychopathy, which, although too complex to discuss here, does not appear unreasonable. Doren contends that antisocial personality disorder is a measure of criminality but that his concept of psychopathy is more restricted, covering only about half of those with antisocial personality.

To determine the validity of this concept of sociopathy, a valid instrument to measure it would have to be developed and used in appropriate epidemiological studies.

The second part of the book deals with treatment issues regarding the psychopathic patient. The underlying argument that Doren wishes to make is that these patients can be taught to conform their goal-directed behavior to achieve more socially acceptable goals and that this would be a major achievement and of benefit to society. He poses this argument against the idea that psychotherapy and development of social skills only make psychopathic patients better psychopaths. However, Doren concedes that psychopathic patients can never develop the object relations that nonpsychopathic individuals can develop.

On a more nuts and bolts level Doren describes such treatment issues as the accuracy of historical information, early differential diagnosis of psychopathy, psychotherapeutic "traps" to avoid, and direct and indirect methods that psychopathic patients use to try to control their environment. These issues and techniques are described in a clear and understandable fashion and include techniques I have not read about elsewhere (although this may merely reflect my relative lack of experience with this population). For example, Doren recommends not focusing on the truth or falsity of situations related in therapy by psychopathic patients but, rather, dealing with the general issues involved. His feeling is that important themes will be repeated and can be worked with even if specific stories cannot be trusted.

This is a well-written and interesting book that would be worth the time of those mental health professionals who work with predominantly antisocial or psychopathic populations.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Dystonic Reactions to Amitriptyline and Doxepin

SIR: Although most clinicians associate extrapyramidal reactions with neuroleptic drugs, they can also occur as a result of antidepressant treatment (1–4). I recently treated a patient whose response to two different tricyclic antidepressants affirms this possibility.

Ms. A, a 30-year-old mother of two, initially presented at age 26 with a 3-month history of nervousness, early insomnia, anorexia, fatigue, depressed mood, and crying spells. She met the *DSM-III* criteria for major depression and was started on a regimen of amitriptyline, 100 mg h.s. The symptoms of her depression improved substantially within 4 weeks. After 3 years of treatment, she became pregnant and discontinued the use of amitriptyline.

Shortly after delivery, Ms. A medicated herself with a single 75-mg dose of amitriptyline in an attempt to overcome her early insomnia. Within hours she developed marked stiffness of her arms and rolling upward of her eyeballs. She did not take any more amitriptyline, and her motor symptoms disappeared within 24 hours. She denied present or past use of neuroleptics as well as personal and family history of neurological disorder.

When Ms. A's depressive symptoms worsened shortly thereafter, treatment with doxepin was started. The dose was increased up to 300 mg h.s. Within hours after the third 300-mg dose, she developed severe dystonic symptoms, including rolling upward of her eyes, twisting of her arms, and stiffening of her tongue. The doxepin was discontinued, and within 24 hours her motor symptoms disappeared.

When her insomnia worsened, Ms. A took a single 150-mg dose of doxepin to help her sleep. Again she experienced oculogyria, twisting of her arms, and stiffening of her tongue. At that point she became convinced that the reaction was due to the medication and she threw it away. The dystonic symptoms disappeared within 24 hours.

Although I did not have the opportunity to observe her reactions myself, Ms. A spontaneously articulated symptoms consistent with dystonia without having any prior knowledge about such reactions; the reaction occurred three times, when she took amitriptyline or doxepin, and disappeared when she stopped them. She did not experience foaming at the mouth, tongue biting, incontinence, or loss of consciousness during these reactions.

Although various extrapyramidal reactions have been linked with some of the more recently introduced atypical antidepressants, including amoxapine, trazodone, and nomifensine, as well as with the monoamine oxidase inhibitors (1–4), to my knowledge this is the first reported case in which a single patient developed dystonic extrapyramidal reactions to two different tricyclic antidepressants, amitriptyline and doxepin.

While the mechanism of extrapyramidal symptoms induced by antidepressants is unknown, it is possible that an acute shift in the balance of dopaminergic and cholinergic neurotransmission in the caudate nucleus or putamen is involved. While the standard tricyclic antidepressants have weak affinities for striatal dopamine receptors and weak ability to block dopamine reuptake, doxepin and amitriptyline are especially anticholinergic and have a wide variety of effects on noradrenergic, serotonergic, histaminergic, and other neurotransmitter receptors (5). Whatever the mechanism, clinicians treating patients with tricyclic antidepressants as well as neuroleptics should be aware that even the typical tricyclic antidepressants may occasionally cause dystonia.

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Neurocutaneous Melanosis and Psychosis

SIR: The association of giant hairy nevi with malignant melanoma of the leptomeninges is uncommon but well recognized; it is referred to as neurocutaneous melanosis (1). Neurological and mental changes can occur in this syndrome (1) but, so far, psychosis has not been described. We should like to discuss the interplay of emerging structural brain disease and administration of a corticosteroid in the etiology of this acute brain syndrome in light of the following case report.

Ms. A, a 26-year-old Caucasian woman, presented with a 3-week history of headache, nausea, and vomiting. She had a giant pigmented hairy nevus covering the bathing trunk area and many smaller lesions over her trunk, limbs, and face. When she was 12 years old, she had developed complex partial seizures with secondary generalization, which were well controlled by carbamazepine. There was no family or personal history of psychiatric illness.

On examination Ms. A was afebrile and photophobic and had neck stiffness. Her pulse was 50 beats/minute and her blood pressure was 120/70 mm Hg. Her cerebrospinal fluid contained atypical neoplastic epithelial cells. CT and nuclear magnetic resonance scans showed lesions near the

> pineal, pituitary, right frontal lobe, and vertex. Two weeks of cranial irradiation, a 48-mg/day dose of dexamethasone, a brief course of opiate analgesia, and domperidone ameliorated her symptoms. During this period she had one generalized seizure.
>
> Over the next 4 weeks, the dexamethasone was reduced to 8 mg/day. Then Ms. A's behavior suddenly changed. She appeared slowed down at first and then became overactive and agitated. Her mood was labile; at times she was frightened and distressed, and at other times she was euphoric and uninhibited. She demonstrated echolalia and perseveration and believed that she was responsible for the deaths of various members of her family. She experienced derealization and terrifying auditory and visual hallucinations. She was disoriented in time and place and had no insight into her mental illness. Small doses of haloperidol and chlorpromazine produced a slight improvement. The dose of dexamethasone was reduced further to 4 mg/day, but headache, vomiting, and neck stiffness returned.
>
> A second CT scan showed hydrocephalus. The dexamethasone was increased to 80 mg/day, and opiate analgesia was reintroduced. The headache and vomiting decreased over the next week, and Ms. A's psychotic symptoms disappeared. Two months later, however, following a recurrence of her physical symptoms, she died.
>
> The post-mortem examination showed mild hydrocephalus, a sparsely pigmented malignant melanomatous infiltrate throughout the subarachnoid space, and hundreds of small intracortical metastases. Both amygdalae were almost entirely replaced by tumor, and there were similar large deposits in the thalami.

A diagnosis of ictus-related psychosis was excluded, since the last seizure had been some 6 weeks earlier. Steroids usually produce an affective (2) or, more rarely, an organic (3) psychosis. Emerging structural brain disease may have rendered the patient more susceptible to a steroid psychosis, but the dose of dexamethasone was actually being reduced when the psychosis developed, and when the dose was increased the psychotic symptoms resolved. The most parsimonious explanation for the psychosis is the rapid growth of the melanomatous cerebral deposits (4). The features of perseveration, echolalia, and disorientation are consistent with a diagnosis of psychosis secondary to coarse brain disease (5).

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Anorexia Nervosa and Parotid Enlargement

SIR: I have recently had the opportunity to observe a 22-year-old man with a 4-year history of anorexia nervosa with bulimic attacks who has had two episodes of remarkable parotid enlargement ("like a hamster").

> Mr. A reported that the first episode had occurred about a year earlier and had lasted for only a few hours. The second episode lasted 1 week, and the patient was referred to our outpatient department by his physician, who wondered whether there was a connection between the eating disorder and the parotid enlargement. Mr. A himself denied having serious eating problems and questioned the need for therapy. He had been in the military service 1 week and claimed that he had been eating normally, without bulimic attacks or vomiting, during that time.
>
> Mr. A did not appear remarkably cachectic. His body weight was just below the ideal weight. Both parotid glands showed a marked symmetrical enlargement. He had no signs of inflammation, no fever, and no pain. His amylase level was high (1800 U/liter) on admission and low (210 U/liter) 2 days later, with low lipase levels (31 U/liter) on both days, indicating that the amylase elevation was of parotid origin. Results of other laboratory tests, including tests for infectious diseases, were normal.

The connection between eating disorder and enlargement of the salivary glands is described in the literature (1, 2). However, the pathological mechanism is unclear. It is possible that malnutrition, protein deficiency, and irritation of the mucous membrane of the mouth by vomiting lead to hypertrophy of the salivary glands. In my opinion it may be helpful to consider a diagnosis of eating disorder in unclear cases of salivary gland enlargement.

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Bowel Obsession Responsive to Clomipramine

SIR: I read with great interest the article about treatment of bowel obsessions with tricyclic antidepressants by Michael A. Jenike, M.D., and associates (1). They used, with good response, imipramine and doxepin. As a complement to that report, I should like to present the case of a patient with such a problem who responded well to clomipramine, a tricyclic antidepressant not yet available in the United States.

> Mr. A, a 21-year-old unmarried student of dentistry, explained to me his deep fear of having a bowel movement in public when he was away from home. He would take four or five trips to the bathroom just before leaving the house. When walking on the street, he was deeply concerned about having a bowel movement, and his sense of security returned only when there was a restroom in the vicinity. This obsession worsened during school examina-

tions and holidays and had an adverse effect on his social life. He had had this problem for at least 7 years. He did not have any depressive symptoms.

Mr. A was started on a regimen of clomipramine, 50 mg/day. Three weeks later he began going to the bathroom just once a day, although some fear still existed. Two months later his fears had disappeared completely and he was symptom free. After 7 months the medication was discontinued, and 9 months later he remained symptom free.

It has been observed that clomipramine has an important antiobsessive effect (2, 3). This case is remarkable to me because a low dose of clomipramine alone produced a good clinical response, although clomipramine has been used in combination with clonidine in low doses (4). This is an isolated case, but I believe it would be of general interest to evaluate further the effect of clomipramine in this kind of obsessive problem.

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Reaction to Chicken Nuggets in a Patient Taking an MAOI

SIR: A number of foods are known to provoke a hypertensive reaction in patients taking a monoamine oxidase inhibitor (MAOI). To our knowledge, the following is the first case of a possible reaction to chicken prepared in nugget form.

Mr. A, a 24-year-old white man, had been having panic attacks since the age of 14. Because his attacks did not respond to up to 350 mg/day of imipramine, his medication was changed to phenelzine. He reported dramatic improvement at a dose of 75 mg/day of phenelzine; he carefully followed prescribed dietary restrictions and did not complain of any side effects.

However, Mr. A reported a reaction after eating chicken nuggets at a restaurant. A few minutes after eating, he felt pressure in his stomach, followed by a severe throbbing vascular headache in his temples. At the same time, he was aware of his heart racing and pounding. These symptoms peaked 15 minutes later and then subsided over the following hour without medical attention. He felt that this episode was quite unlike his panic attacks and volunteered that he had "never had anything like it."

Mr. A called the restaurant in an attempt to discover whether any proscribed substance had been present in his meal. He was told that monosodium glutamate (MSG), an item on his list of dietary restrictions, had been added to the chicken; he himself had observed that the chicken nuggets he ate at the restaurant were spicier than chicken nuggets he had eaten in other restaurants. He did not attempt to eat chicken nuggets again.

This patient appears to have experienced a hypertensive reaction, typical of those seen in patients taking MAOIs (1), after eating chicken nuggets. The reaction seems to have been related to ingestion of MSG, a food additive that may interact with MAOIs (2). Although MSG is also known to cause a reaction called "Chinese restaurant syndrome" in susceptible individuals, the vascular headache experienced by this patient is not a normal part of that syndrome (3).

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Disulfiram and Allergy to Rubber

SIR: Within the general population, the most common causes of allergic rubber dermatitis are the rubber vulcanization accelerators 2-mercaptobenzothiazole and tetramethylthiuram disulfide (1). The usual source of exposure is rubber gloves. Because the dermatitis produced by tetramethylthiuram disulfide and other thiurams can flare up when disulfiram is administered (2–4), patients who are being evaluated for disulfiram therapy should be routinely asked about allergy to rubber. The following case illustrates the importance of following up a positive history of rubber dermatitis with patch testing to clarify the specific source of the dermatitis.

Mr. A, a 25-year-old married white construction worker with chronic alcohol abuse, was referred for evaluation for a trial of disulfiram treatment. His medical history was notable only for a pruritic, erythematous, edematous rash that developed on both of his hands a few hours after he wore rubber gloves. A patch test was ordered and revealed that the patient reacted strongly to a 2% mercapto mix (containing 2-mercaptobenzothiazole and other mercaptans) but not to a 1% thiuram mix (containing tetramethylthiuram disulfide, disulfiram, and other thiurams). Mr. A was subsequently treated with disulfiram without dermatologic complications.

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REM Sleep Behavior Disorder

SIR: The report by Albert Hefez, M.D, and associates (1) about the effects of extreme stress on sleep describes a sea disaster survivor who "showed complex motor activity during REM, which at one time resulted in an actual escape from the bedroom." This 20-year-old man also vocalized, had violent behaviors, and twice fell out of bed during REM sleep. He had nightmares in which he "relived" the sea disaster, which had happened 6 months previously. This case satisfies diagnostic criteria for REM sleep behavior disorder, which is usually a chronic, progressive parasomnia involving variable loss of electromyographic atonia during REM sleep and emergence of complex and violent behaviors, often resulting in substantial injury (2–4). Data from the first 30 patients in our sleep disorders center indicate that REM sleep behavior disorder chiefly affects older men (the mean age at onset is 60 years) and has a major neurological cause (e.g., dementia, stroke) in 40% of cases and an unknown cause in 60%.

We recently identified the case of Mr. A, a 67-year-old man whose chronic REM sleep behavior disorder had appeared 27 years previously during a very stressful divorce. There was no history of earlier sleep or psychiatric disturbance. For 1 year after the divorce, the patient suffered from what, in retrospect, was a severe adjustment disorder with depressed mood, but he did not receive treatment. He would jump out of bed and throw punches while dreaming of being attacked by animals or unfamiliar people. He did not recall dreaming about his first wife or about their divorce. When he remarried 3 years later, his second wife immediately noticed his wild sleep behaviors. In one episode, he put her head in an armlock and punched her repeatedly while he was dreaming.

Mr. A and his second wife were happily married and he was generally regarded as having a pleasant disposition. He had not consumed ethanol for 30 years because it caused headaches. The results of neurological and psychiatric evaluations were unremarkable. Polysomnography established the diagnosis of REM sleep behavior disorder. Treatment with clonazepam controlled the nightmares and problematic sleep behaviors, which is the usual therapeutic response with patients who have REM sleep behavior disorder.

In neither this case nor the one described by Dr. Hefez and his colleagues (1) was polysomnography done before the stressful event; that is, there was no premorbid comparison sleep study. However, these cases suggest that extreme or major stress can chronically alter skeletal motor processes during REM sleep to an extent that is clinically relevant.

In another case, a 40-year-old chemical dependency counselor was given a diagnosis of REM sleep behavior disorder 11 years after its onset was precipitated by abstinence from longstanding ethanol and amphetamine abuse. There was no other psychiatric history. A urine toxicology screen was negative during our evaluation. Clonazepam was superior to other psychotropics in controlling the disorder. Both ethanol and amphetamine suppress REM sleep, so this case could represent a distinct form of pathological REM rebound that persists during prolonged sobriety. An acute form of REM sleep behavior disorder can accompany withdrawal from ethanol and sedative-hypnotic abuse (5). Furthermore, we have documented the acute onset of REM sleep behavior disorder in a 67-year-old woman 1 week after rapid withdrawal from imipramine.

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Psychiatric Illness at All Stages of Human Immunodeficiency Virus Infection

SIR: There have been a number of reports describing psychiatric findings in patients with acquired immune deficiency syndrome (AIDS) and AIDS-related complex, the late stages of human immunodeficiency virus (HIV) infection. Depression, dementia, organic psychoses, mental dullness, concentration problems, adjustment disorder, and personality change have been most commonly reported (1–3).

Our medical center is the medical evaluation facility for all U.S. Air Force members who develop HIV infection. Most of the patients are apparently seen early in the course of infection, are symptomatic, and have normal or minimally impaired immunologic function in vivo. Reports of psychiatric disorders in this group of patients are lacking.

Between Jan. 1, 1986, and Aug. 31, 1987, there were 536 admissions at our center for medical evaluation of HIV seropositive persons. In a retrospective record review, it was found that 111 of these patients had been seen by the psychiatric consultation service. There were 42 requests to evaluate patients for possible cognitive deficits, 28 for depression, 14 for coping difficulty, nine for anxiety, and 18 for other reasons.

The following *DSM-III-R* axis I diagnoses were made: no axis I diagnosis (N=71, 64.0%), adjustment disorder (N=24, 21.6%), alcohol abuse (N=12, 10.8%), major depression (N=4, 3.6%), organic mental disorder not otherwise specified (N=4, 3.6%), dysthymia (N=2, 1.8%), and organic mood disorder (N=2, 1.8%). Seventeen patients with no axis I diagnosis (15.3% of the 111) were treated for V code conditions. Twenty (18.0%) of the patients received personality disorder diagnoses: passive-aggressive (N=5, 4.5%), histrionic (N=3, 2.7%), narcissistic (N=3, 2.7%), avoidant (N=3, 2.7%), antisocial (N=2, 1.8%), dependent (N=1, 0.9%), schizoid (N=1, 0.9%), and mixed (N=1, 0.9%).

Only nine of the 111 patients seen by the consultation service had been aware for more than 3 months that they were HIV seropositive. All nine were in the hospital for periodic reevaluations. Five of those nine patients received axis I diagnoses (adjustment disorder in four and alcohol abuse in one). One received an axis II diagnosis of narcissistic personality disorder. Three had made suicide attempts between initial evaluation and reevaluation. Only two of the nine had received psychiatric consultation during the initial evaluation, and neither was thought to have a psychiatric disorder at the time.

The 111 patients included 14 with AIDS and AIDS-related complex. They received nine axis I diagnoses: adjustment disorder (N=5), alcohol abuse (N=2), organic mental disorder not otherwise specified (N=1), amphetamine abuse (N=1). Three personality disorder diagnoses were given: narcissistic, schizoid, and passive-aggressive.

Our findings suggest that with the passage of time and progression of HIV infection, the potential for psychiatric illness increases. For diagnostic, prognostic, and therapeutic purposes, it is important to consider the relative roles of CNS effects of HIV-related illness, psychiatric predisposition, and cumulative effects of chronic stress. The patients we have seen so far have been notable for their lack of cognitive abnormalities in the early stages of HIV infection and for development of psychopathology during the period of time between initial evaluation and reevaluation. We plan a prospective study that will compare *DSM-III-R* axes I, II, IV, and V assessments over time with immunologic factors, CSF parameters, scores on several psychiatric rating scales, neuropsychological test results, standard mental status examination findings, and responses to treatment.

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Use of Animals in Research

SIR: One of our papers (1) was cited in a letter to the Editor (2) to support the position that many animal tests have served no purpose in the development of major antidepressant treatments. Our position on this issue, to which we have devoted some years of careful thought and research efforts, is quite different. We called, in that paper and elsewhere, for more *sophisticated* use of animal models, not their replacement. A need for a movement away from the classical "reserpine-depletion" behavioral model for screening potential antidepressants and toward more pharmacologically modern methods was the key theme of the paper. The contribution of brain preparations from appropriate animals in the development of understanding of pre- and postsynaptic receptor mechanisms opens the door to direct examination of effects of new antidepressant drugs on the brain. In the cited article we explicitly described these developments and recommended them as the basis of future animal study.

Dr. Reines, the author of the letter to the Editor, claimed that serendipity alone, based on clinical experience with patients, has led to psychopharmacological treatments. This ignores the crucial examples of the development of lithium and carbamazepine mentioned in the editorial by Pincus et al. (3) and the recent rapid developments in basic neuroscience, which promise to be the basis of psychiatric as well as veterinary progress in diagnosing and treating disease. It also ignores the noteworthy success of preclinical screening of putative psychotropic drugs, using animals, as a predictor of adverse side effects before introducing a substance into clinical practice with humans, thereby substantially lowering the risk of human exposure.

In calling the editorial's focus on the animal rights movement a "straw man," Dr. Reines ignored the central point of the editorial, which documented the clear threat to progress in knowledge and treatment of human disease posed by the animal rights movement. Dr. Reines's letter, which does not admit any possible benefits of animal studies, is an exercise in sophistry, twisting our arguments and those of others in order to serve a purpose which subordinates human welfare to other considerations.

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Haloperidol in Neuroleptic Malignant Syndrome

SIR: In view of the small number of prospective studies on neuroleptic malignant syndrome, the article by Paul E. Keck, Jr., M.D., and associates (1) was a significant and timely contribution. Although their observations focused on the frequency and presentation of the syndrome, their data included another important finding. According to these authors, haloperidol was responsible for 66% of all the cases of neuroleptic malignant syndrome that occurred in 18 months among 679 patients treated with neuroleptics at McLean Hospital. When these data are added to the retrospective data presented in a previous study by these authors (2), the accumulated frequency of haloperidol among the agents that caused definite neuroleptic malignant syndrome within 30 months at the same hospital is 50% (six of 12 patients). The high frequency of neuroleptic malignant syndrome resulting from use of haloperidol has been recognized by other authors, although differently understood (3, 4). Levenson (3) argued that this high frequency reflects the actual use of haloperidol in clinical practice. On the other hand, Sternberg (5) suggested that the frequent use of this drug in "rapid neuroleptization" could be responsible for the high frequency of haloperidol-induced neuroleptic malignant syndrome.

In a recent survey of 129 publications from 1959 to 1987 representing 202 case reports, we found that haloperidol was involved in 99 (49.5%) of all the episodes. Indeed, haloperidol was the most frequent offender—present in 39.0% of all the reported episodes of neuroleptic malignant syndrome published before 1980 and in 47.2% of all the episodes from 1980 to 1983. In addition, haloperidol was given in higher average doses and was associated with a significantly lower (4.5%–7.0%) rate of mortality.

The question remains whether the use of haloperidol involves a greater risk of neuroleptic malignant syndrome, that is, whether its prevalence among patients with neuroleptic malignant syndrome is higher than its rate of use in clinical practice. Up until now, we were forced to rely on comparisons between different populations; for example, in a sample of 15,695 patients, Baldessarini et al. (6) found that the rate of haloperidol use was 20.5%, as opposed to a frequency of 47.2% for haloperidol use in cases of neuroleptic malignant syndrome during the same period. By comparing the rate of use of haloperidol in their hospital with its frequency as the offender in neuroleptic malignant syndrome, Dr. Keck and associates could provide us with substantial information on this subject and make a valuable contribution to our understanding of the circumstances in which neuroleptic malignant syndrome occurs.

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Dr. Keck and Associates Reply

SIR: Drs. Shalev and Ursano raise the important question of whether haloperidol poses a greater risk of neuroleptic malignant syndrome than do other neuroleptics. In response to their query, we have reviewed the frequency of use of haloperidol at our institution over the 30-month interval encompassed by our two surveys of the frequency of neuroleptic malignant syndrome. In the total cohort of approximately 1,162 patients treated with neuroleptics, 21% received haloperidol. Haloperidol was implicated as the offending neuroleptic in six (35%) of the episodes of neuroleptic malignant syndrome reported in our two surveys. (Although Drs. Shalev and Ursano cite 12 patients as having neuroleptic malignant syndrome in these surveys, there were actually 17 episodes of neuroleptic malignant syndrome occurring in 14 patients.)

Although it is tempting to attribute a greater risk of neuroleptic malignant syndrome to treatment with haloperidol on the basis of this comparison and the findings of Drs. Shalev and Ursano in their review of published cases, several questions remain. First, dissimilar dosing practices, in which haloperidol is given in higher average doses than low-potency neuroleptics—cited by Drs. Shalev and Ursano and supported by the earlier findings of Baldessarini et al.—coupled with a high frequency of haloperidol use could explain this apparently greater risk.

Second, Addonizio et al. (1) have recently suggested that the rate of increase of the dose of neuroleptic may be an important factor in the induction of neuroleptic malignant syndrome. Since haloperidol is a high-potency neuroleptic, rapid increases in doses of haloperidol, as opposed to a low-potency agent, may more rapidly lead to high neuroleptic exposure. A case-control study might more definitively address the roles of neuroleptic potency, dose, and rate of dose increase in the induction of neuroleptic malignant syndrome. We have begun to analyze our data in hopes of better understanding these factors.

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PAUL E. KECK, JR., M.D.
HARRISON G. POPE, JR., M.D.
SUSAN L. MCELROY, M.D.
Belmont, Mass.

Too Many Psychiatrists?

SIR: Recently, my residents, most of whom are graduates of foreign medical schools, discussed the article by Joel Yager, M.D., and Jonathan F. Borus, M.D., "Are We Training Too Many Psychiatrists?" (1), in which fears about the possible diminution of incomes of private psychiatrists and university departments of psychiatry were expressed. The residents questioned the appropriateness of such a reaction. They felt that a dearth or surplus of psychiatrists should be evaluated on the basis of patients' needs rather than psychiatrists' incomes. (In their defense I must say that the residents are all young and naive.) However, even accepting the economic thrust of the article, it is based on supply-side economics, which, to paraphrase John Stuart Mill, states that there will always be individuals in a society who do not have the means to obtain the things they need, and these people are not the concern of legislators (2). Mill meant that supply will regularly and naturally grow to meet demand. A corollary of this is that demand will remain at a high level if supply is limited.

The morality of this position is beside the point; its validity is the concern, for there are other economists, Keynsian in type, who dispute the theory. My residents questioned whether we should claim that the psychiatric sky is falling on the basis of an economic theory about which we are not expert and on which experts disagree. Although they were taken with the colorful airline pilot training metaphor in the article, they thought it was a bit far-fetched. I would suggest another analogy, with which these residents are more familiar: the mohel, or ritual circumciser. While not Board-certified in surgery, mohels perform one necessary procedure and have been doing it in a most effective manner for several centuries. If it should happen that a few mohels become Board-certified urologists, who should complain? Perhaps it is better that the many patients in our public system have physicians with limited training in the field of psychiatry rather than physicians with no training at all or, even worse, no physicians at all. And if a few of these nonacademic residents pass their Board examinations and go into private practice, who should complain?

My residents felt that Drs. Yager and Borus were taking psychiatry too "gentle into that good night." Instead of closing programs, we should be helping weak ones become strong. Instead of driving out your trainees, we should provide opportunities for the best and brightest, from here and abroad. I agree with my residents. I wonder whether the authors really believe that our country benefits by depriving young people such as these of the opportunity it so proudly offered to generations who came before.

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1. Yager J, Borus JF: Are we training too many psychiatrists?, Am J Psychiatry 1987; 144:1042–1048
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MARVIN H. LIPKOWITZ, M.D.
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Drs. Yager and Borus Reply

SIR: Once again we are grateful for the opportunity to reemphasize what we did and did not say in our article. We are *not* primarily concerned with the fact that an excessive number of psychiatrists may bring about a drop in psychiatrists' incomes; that is a relatively minor point. We *are* primarily concerned about the quality of care provided by psychiatrists and their shifting roles in relation to the growing numbers of other mental health professionals. We ardently wish that all those who need and desire competent psychiatric care could obtain it, not just those who can afford it. However, we hope that the care they receive is competent—not substandard care passed off as representative of what our profession has to offer. We are not suggesting that we should limit the number of psychiatrists in order to keep demand at a high level. We do suggest limiting trainees to the number we can actually train to be competent and attesting to the competence of our graduates by requiring them to successfully complete excellent training programs *and* certification examinations. We fully agree with Dr. Lipkowitz that weak programs should be strengthened, but we do not believe that residents who fail to demonstrate proficiency should be excused by the profession because we need more psychiatrists.

We thank Dr. Lipkowitz for the analogy of the mohel, and we will gladly use it. Certainly, no one tries to pass off all mohels as fully competent in urology, whereas poorly trained psychiatrists *are* passed off as fully competent to practice psychiatry in an unlimited manner. Our major concern is ensuring competence in whatever training is accomplished. Even mohels these days must undertake a rigorous academic and clinical curriculum and pass certifying examinations to demonstrate competence in their limited but delicate area of expertise. In concluding, we would like to rephrase our prior question about airline pilots using Dr. Lipkowitz's analogy: would he and his residents really be willing to put their foreskins on the block of a mohel whose training was substandard and whose competence was uncertain?

JOEL YAGER, M.D.
Los Angeles, Calif.
JONATHAN F. BORUS, M.D.
Boston, Mass.

Differences Among Patients With PTSD

SIR: Bernard Lerer, M.D., and colleagues made a laudatory effort in their article "Cyclic AMP Signal Transduction in Posttraumatic Stress Disorder" (1) to demonstrate that a biological marker associated with major affective disorders exists in patients with posttraumatic stress disorder (PTSD). Their findings suggesting a receptor-mediated functional deficit in patients with PTSD, similar to that found in depressed patients, complement other recent biological marker findings in PTSD patients (2). Because of recent clinical observations of our own, we were surprised that Dr. Lerer and colleagues found positive results in such a small number of heterogeneous subjects. Their study sample was composed of patients who could be divided into three distinct PTSD groups on the basis of the type of trauma to which they had been subjected. Five of the patients had experienced military combat; four, terrorist activity; and three, motor vehicle accidents.

In contrast to these authors' biological observations, our clinical observations are being confined to a much larger sample of two types of PTSD patients diagnosed according to *DSM-III-R* criteria: patients whose conditions were precipitated by either motor vehicle accidents or Vietnam War combat experiences. The groups include more than 70 and 150 patients, respectively. Preliminary analyses of these two PTSD groups demonstrate major differences on many variables, including age; sex; socioeconomic level; the nature, timing, frequency, and duration of the stressor; treatment compliance behavior; and the character of intrusive and avoidance symptoms. More specifically, our PTSD combat veterans experienced lengthy periods of intense combat involving physical deprivations and multiple losses. These traumas occurred during the patients' adolescence or early adulthood and are in stark contrast to the nature and duration of the experiences suffered by the PTSD motor vehicle accident patients and their ages at the time of their accidents. Moreover, the clinical presentations of the two groups of patients are considerably different. For example, the intrusive symptoms of combat veterans often include dissociative experiences, while those of motor vehicle accident patients are more typified by illusions.

These preliminary differences are of sufficient magnitude and quality and call into question the feasibility of constructing generalizations about PTSD. From a research perspective, we believe attempts to identify biological, psychophysiological, and biochemical correlates of the syndrome will be more fruitful if they are limited to PTSD patients who are homogeneous in terms of the trauma they experienced. Although their findings were negative, Kudler et al. (3) used this approach in a recent study demonstrating that cortical nonsuppression is rare in PTSD combat veterans when no concomitant major depression is present. Similarly, Kolb (4) recently elaborated a neuropsychological hypothesis to explain PTSD but confined his observations to military veterans who had experienced long and high-level combat exposure. Because of the heterogeneity of their sample, the positive findings of Dr. Lehrer and colleagues appear rather remarkable and serendipitous. We wonder whether a reexamination of their data, grouped on the basis of the type of trauma experienced by their patients, would facilitate the further delineation of the biological concomitants of the posttraumatic syndrome and its subtypes.

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4. Kolb LC: A neuropsychological hypothesis explaining posttraumatic stress disorders. Am J Psychiatry 1987; 144:989–995

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ALLAN BURSTEIN, M.D.
Freehold, N.J.
ROBERT A. GREENSTEIN, M.D.
Philadelphia, Pa.

Dr. Lerer Replies

SIR: My colleagues and I are somewhat puzzled by the description of our findings as "serendipitous" as well as the product of a "laudatory effort." To refer to them as both is an obvious contradiction. The hypothesis that PTSD and affective disorder may share biological characteristics was, in fact, clearly stated in the introduction to our paper and was tentatively supported by the results presented. The reason for this was the important question raised, and we alluded to it in the discussion of our findings.

We fully agree with the comments of Dr. Ciccone and associates about the heterogeneity of PTSD and the consequent implications for biological marker studies. Our study did in fact follow the approach of Kudler et al.; we subdivided the subject group according to the presence or absence of concomitant *DSM-III* diagnoses (major depression and generalized anxiety disorder). Cyclic AMP signal transduction was significantly reduced in both subgroups. Subdivision according to the nature of the experienced trauma also revealed no differences, although the small sample size did not permit a definitive examination of the suggestions of Dr. Ciccone and colleagues in this regard.

The background and clinical differences between PTSD combat veterans and PTSD motor vehicle accident patients that Dr. Ciccone and associates have noted are of considerable interest. We suggest, however, that resolution of the heterogeneity problem in PTSD demands an approach focused primarily on empirical delineation of a "core" PTSD syndrome defined according to clinical characteristics. Our experience (1, 2) indicates that trials of antidepressant medication in PTSD patients are also rendered problematic by the heterogeneous population encompassed by the *DSM-III* criteria, even in their revised form. Complicating factors such as alcohol and substance abuse, compensation issues, and concomitant affective and anxiety symptoms should also be addressed in this context. Cross-cultural comparisons would greatly enhance a study of this type.

The critical issue is whether PTSD is indeed an independent entity or whether it is a complex of symptoms shared by individuals with a variety of diagnoses (including affective disorder) who have in common previous exposure to psychologically traumatic events. Samples focused on posttrauma subjects with affective characteristics would be more likely to manifest the biological markers also found in affective patients and to respond to antidepressant medication. Presently available data are insufficient to address these issues. Further neurobiological characterization of PTSD obviously depends on the generation of such data.

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1. Lerer B, Bleich A, Garb R, et al: Posttraumatic stress disorder in Israeli combat veterans: effect of phenelzine treatment. Arch Gen Psychiatry 1987; 44:976–981
2. Shestatzky M, Greenberg D, Lerer B: A controlled trial of phenelzine in posttraumatic stress disorder. Psychiatry Res (in press)

BERNARD LERER, M.D.
Jerusalem, Israel

Reprints of letters to the Editor are not available.

Calendar

(Continued from page A28)

August 21–25, 8th International Congress of International Association for the Scientific Study of Mental Deficiency, Dublin. Contact Mr. John O'Gorman, Congress Chairman, 8th World Congress, I.A.S.S.M.D., 12, Pembroke Park, Dublin 4, Ireland.

August 23–28, annual meeting, American Association for Partial Hospitalization, Denver. Contact Joan Fridberg, Administrative Coordinator, 1221 Massachusetts Ave., N.W., Suite 3, Washington, DC 20005; 202-347-1649.

August 24–28, annual meeting, American Sociological Association, Atlanta. Contact Jen L. Suter, Meetings and Marketing Manager, 1722 N St., N.W., Washington, DC 20036; 202-833-3410.

August 30–September 4, XXXI International Congress on the History of Medicine, Bologna, Italy. Contact Organizing Secretariat, Conference Service, Via Tagliapietre, 18/B, 40123 Bologna, Italy; 051-331466; Telex 213616 BO I.

SEPTEMBER

September 4–9, 10th International Congress on Criminology, Hamburg, F.R.G. Contact Congress Secretariat, HMC Congress Organisation, 10th Int. Congr. Crimin., P.O. Box 30 24 80, D-2000 Hamburg 36, F.R.G.; 040-35-69-22-42; Telex 212 609, Telefax 35 69 21 80.

September 4–9, 17th European Conference on Psychosomatic Research, Marburg, West Germany. Contact Prof. Dr. med. Wolfram Schuffel, Psychosomatic Division, Centre of Internal Medicine, University of Marburg, D-2550 Marburg, West Germany.

September 7–11, Fall Components Meeting, American Psychiatric Association, Washington, D.C.

September 12–17, IVth International Conference of Psychophysiology, Prague. Contact Association of Czechoslovak Medical Societies, J.E. Purkyne, IVth I.C.P., P.O. Box 88, CS-120 26 PRAHA 2, Czechoslovakia; Telex 121293.

September 14–17, Fourth International Conference of the Marce Society, The Family, Childbearing and Mental Illness, University of Keele, England. Contact Marce Society Secretariat, Bell Howe Conferences, Gothic House, Barker Gate, Nottingham, NG1 1JU, England; 0602-410679.

September 17, International Symposium on Sleep Disorders, Sao Paulo, Brazil. Contact Rubens Reimao, M.D., Rue Glicineas 128, 04048 Sao Paulo, SP, Brazil.

September 21–23, II Panamerican Sleep Congress, Buenos Aires. Contact Enrique Soltanik, M.D., Ju[illegible] 171, 141[illegible] Buenos Aires, Argentina.

September 22, interim meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 23–25, child psychiatry examination, American Board of Psychiatry and Neurology, Washington, D.C. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

September 23–26, annual meeting, Royal College of Physicians and Surgeons of Canada, Ottawa. Contact Dr. J.[illegible] Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario, Canada K1M 1P4; 613-746-8177.

September 25–28, annual meeting, Alcohol and Drug Problems Association of North America, Inc., Charlotte, N.C. Contact Karst J. Besteman, Executive Director, 444 N. Capitol St., N.W., Suite 181, Washington, DC 20001; 202-737-4340.

September 25–28, annual meeting, Association of Mental Health Administrators, St. Louis. Contact [illegible]re Paul, Director, 840 North Lake Shore Dr., Suite 1103, Chicago, IL 60611; 312-943-2751.

September 26–29, annual meeting, American College of Emergency Physicians, New Orleans. Contact Collin C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 26–29, annual meeting, World Medical Association, Vienna. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 50-40-75-75.

September 28–30, annual meeting, Canadian Psychiatric Association, Halifax, Nova Scotia, Canada. Contact Lea C. Metivier, Chief Administrative Officer, 294 Albert St., Suite 204, Ottawa, Ontario, Canada K1P 6E6; 6[illegible] 235-2[illegible]15.

September 28–October 1, annual meeting, American School Health Association, Lake Buena Vista, Fla. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

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WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

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Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnestic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

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Caution: Federal law prohibits dispensing without prescription. B-4-S

References:

1. Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1982;44(11):401-406.
2. Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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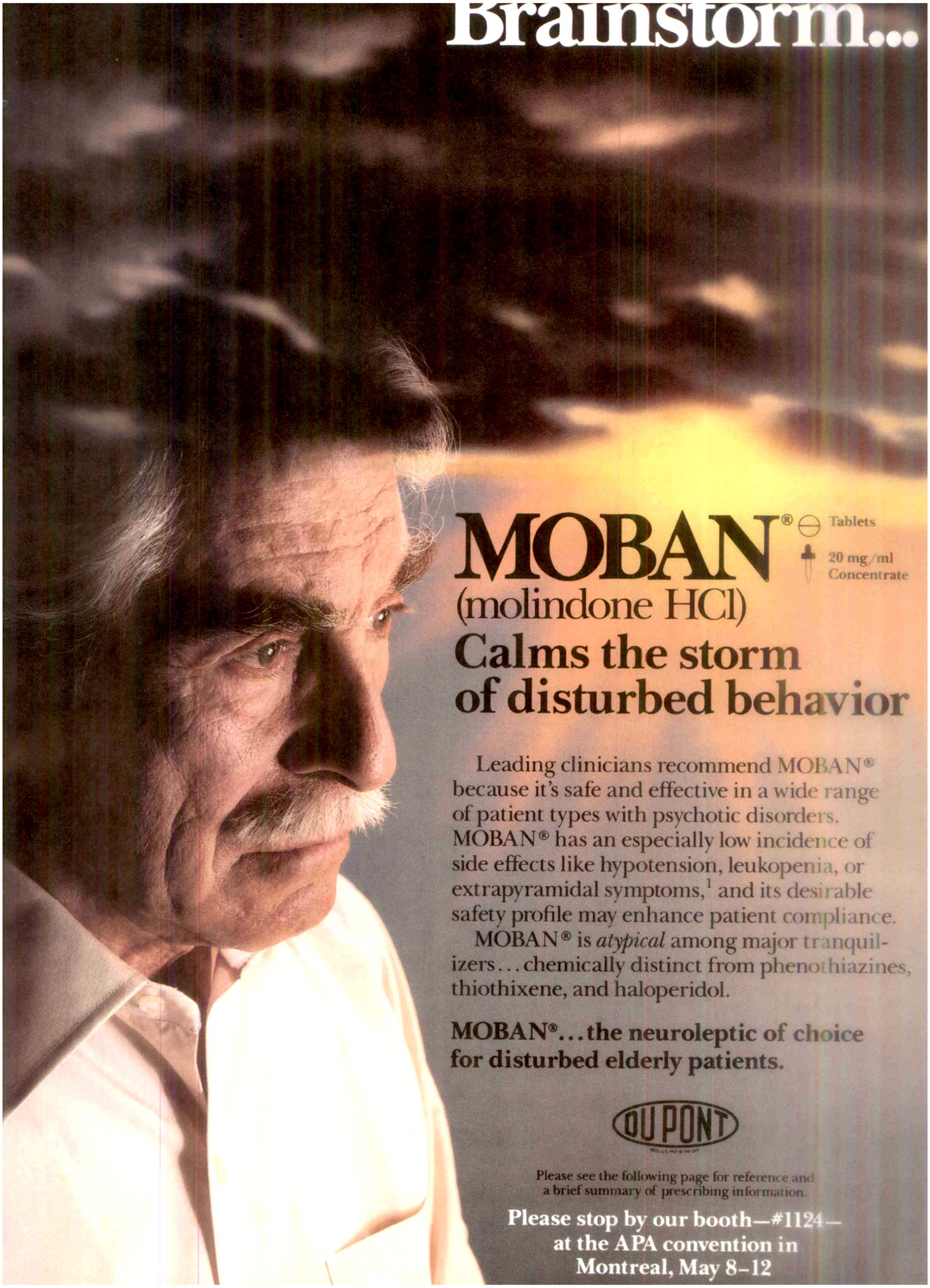

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Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

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PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS Effects: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms. One patient being treated with MOBAN experienced priapism which required surgical intervention, apparently resulting in residual impairment of erectile function.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

Concentrate: 20 mg/ml in 4 oz (120 ml) bottles.

Reference: 1. Peper M: Clinical experience with molindone hydrochloride in geriatric patients. *J Clin Psychiatry* 1985; 46 (sec 2): 26-29.

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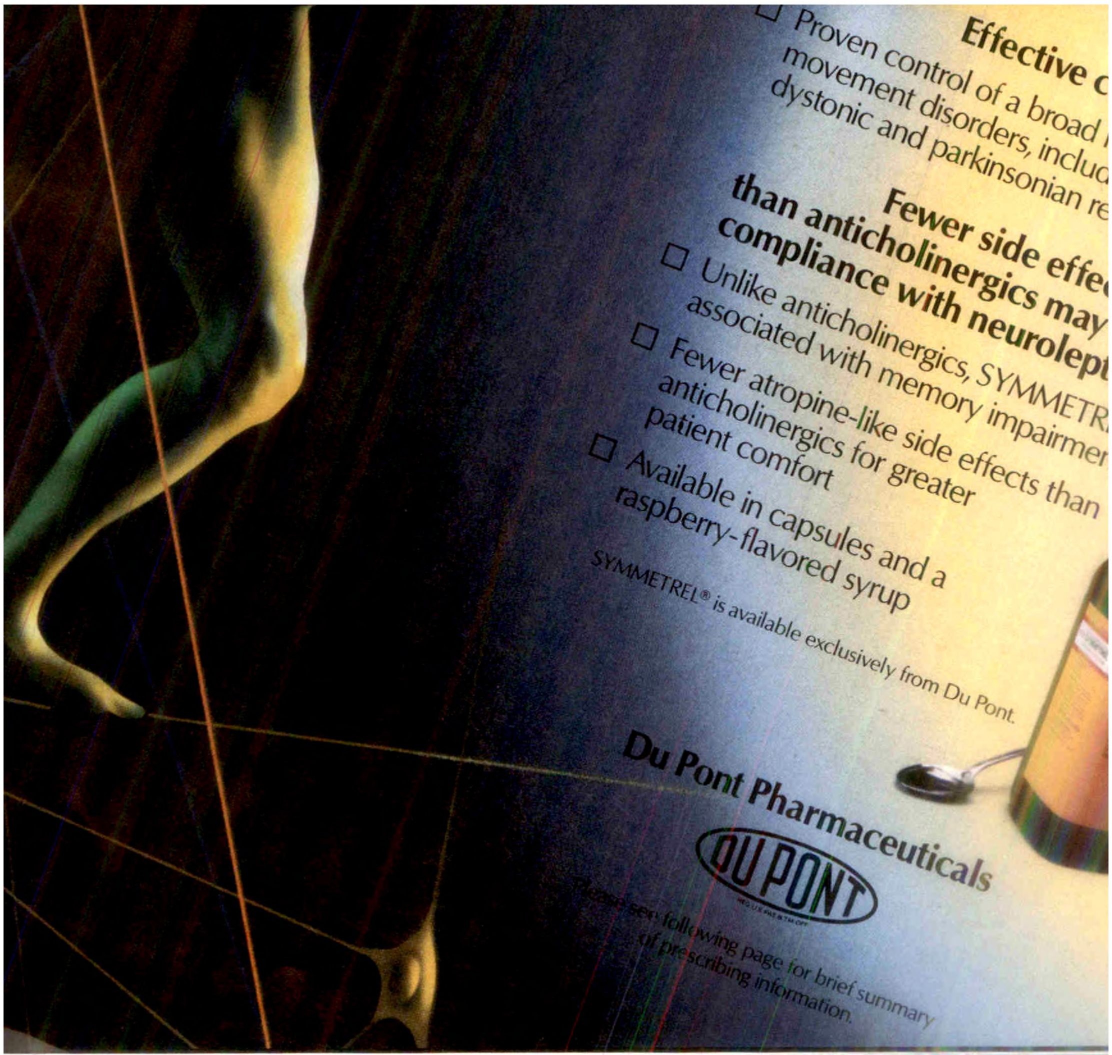

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATION: Drug-induced Extrapyramidal Reactions: SYMMETREL (amantadine hydrochloride) is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with the anticholinergic antiparkinson drugs.
CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.
PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.
Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.
Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.
ADVERSE REACTIONS: The adverse reactions reported most frequently (5—10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1—5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1—1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.
OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.
DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.
HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

Bottles of 100	NDC 0056-0105-70
Bottles of 500	NDC 0056-0105-85
Hospital Unit-Dose Blister Package of 100	NDC 0056-0105-75

As a syrup (each 5 ml [1 teaspoonful] contains 50 mg amantadine hydrochloride) in:

16 oz. (480 ml) bottles	NDC 0056-0205-16

Store at controlled room temperature (59°—86°F, 15°—30°C).

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702 and Banner Gelatin Products Corp., Chatsworth, California 91311, for Du Pont Pharmaceuticals.

References:
1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: amantadine versus benztropine. *World J Psychosynthesis* (special issue) 1984-1985; 16:40-43. **2.** McEvoy JP, McCue M, Spring B, et al: Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry* 1987; 144(5):573-577.

* D.F. Casey, *N. Engl. J. Med.* 298:516. 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

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The successful candidate will be the director of a 30-bed Schizophrenia Unit at the Regional Psychiatric Centre, and responsible for the development of the service, teaching programs for psychiatric residents and fourth year medical undergraduates, and the development of clinical research. The Academic Psychiatrist will divide his time between the Regional Psychiatric Centre and the Schizophrenia Service of the University of British Columbia, Health Sciences Centre Hospital, Department of Psychiatry. This latter service has an inpatient day program, outpatient and community components dedicated to service, teaching and research in Schizophrenia, with access to sophisticated research technologies.

Academic rank and remuneration will be commensurate with qualifications.

The appointment is subject to final budgetary approval. Applications, including a curriculum vitae and name of three referees, should be sent to: Dr. James E. Miles, Head, Department of Psychiatry, The University of British Columbia, 2211 Westbrook Mall, Vancouver, B.C., Canada, V6T 2B5.

In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada.

Books Received

Handbook of Behavioral Medicine for Women, by Elaine A. Blechman and Kelly D. Brownell. Oxford, Pergamon Press, 1988, 451 pp., $75.00.

Women, Power, and Therapy: Issues for Women, edited by Marjorie Braude. New York, Haworth Press, 1988, 340 pp., $29.95.

Teaching Child Management Skills, by Richard F. Dangel and Richard A. Polster. Oxford, Pergamon Press, 1988, 151 pp., $22.50; $12.95 (paper).

Taming Monsters, Slaying Dragons: The Revolutionary Family Approach to Overcoming Childhood Fears and Anxiety, by Joel Feiner, M.D., and Graham Yost. New York, Arbor House (William Morrow), 1988, 282 pp., $16.95.

Self and Others: Object Relations Theory in Practice, by N. Gregory Hamilton, M.D. Northvale, N.J., Jason Aronson, 1988, 330 pp., $30.00.

Child Psychotherapy: Developing and Identifying Effective Treatments, by Alan E. Kazdin. Oxford, Pergamon Press, 1988, 144 pp., $22.50; $12.95 (paper).

Women in Therapy: Devaluation, Anger, Aggression, Depression, Self-Sacrifice, Mothering, Mother Blaming, Self Betrayal, Sex-Role Stereotypes, Dependency, and Work and Success Inhibitions, by Harriet Goldhor Lerner, Ph.D. Northvale, N.J., Jason Aronson, 1988, 285 pp., $27.50.

Improving Mental Health Services: What the Social Sciences Can Tell Us, edited by David Mechanic. San Francisco, Jossey-Bass, 1987, 128 pp., $12.95 (paper).

The New Harvard Guide to Psychiatry, edited by Armand M. Nicholi, Jr., M.D. Cambridge, Mass., Belknap Press (Harvard University Press), 1988, 827 pp., $45.00.

Treating Women's Fear of Failure, edited by Esther D. Rothblum and Ellen Cole. New York, Haworth Press, 1988, 105 pp., $14.95.

The Psychology of Rigorous Humanism, 2nd ed., by Joseph F. Rychlak. New York, New York University Press (Columbia University Press, distributor), 1988, 543 pp., $40.00.

Children in Residential Care: Critical Issues in Treatment, edited by Charles E. Schaefer, Ph.D., and Arthur J. Swanson, Ph.D. New York, Van Nostrand Reinhold, 1988, 283 pp., $[illegible]2.95.

Post-Traumatic Stress Disorder: Diagnosis, Treatment, and Legal Issues, 2nd ed., by C.B. Scrignar, M.D. New Orleans, Bruno Press, 1988, 330 pp., $49.95; $32.95 (paper).

Fundamentals of Endocrinology, by W. Roy Slaunwhite, Jr. New York, Marcel Dekker, 1988, 402 pp., $45.00.

Mainstay: For the Well Spouse of the Chronically Ill, by Maggie Strong. Boston, Little, Brown and Co., 1988, 312 pp., $16.95.

Antarctic Psychology: New Zealand Department of Scientific and Industrial Research Bulletin 244, by A.J.W. Taylor. Wellington, Science Information Publishing Centre, 1987, 1[illegible]7 pp., $41.00 (paper).

The Need to Have Enemies and Allies: From Clinical Practice to International Relationships, by Vamik D. Volkan, M.D. Northvale, N.J., Jason Aronson, 1988, 289 pp., $[illegible]5.00.

Impact of Functional Imaging in Neurology and Psychiatry, edited by J. Wade, S. Knežević, V.A. Maximilian, Z. Lubrin, and I. Prohovnik. London, John Libbey & Co., 1987, 1[illegible]6 pp., $46.00.

Neurology for Non-Neurologists, 2nd ed., edited by Wigbert C. Wiederholt, M.D. Philadelphia, Grune & Stratton (W.B. Saunders Co., Harcourt Brace Jovanovich), 1988, 339 pp., $39.50.

RESOURCES

The Epilepsy Foundation of America's National Epilepsy Library and Resource Center offers current information to physicians and patients. We provide access to:

- TEXTRACT, an in-house database on medical and psychosocial aspects of epilepsy.
- A library of monographs, journals, symposia and conference proceedings and government publications.
- BRS Information Technologies, an on-line service with access to Medline, Excerpta Medica's EMBASE and other databases.
- MEDLARS, the database service of the National Library of Medicine.
- DIALOG Information Services, which also provides access to a variety of medical databases.

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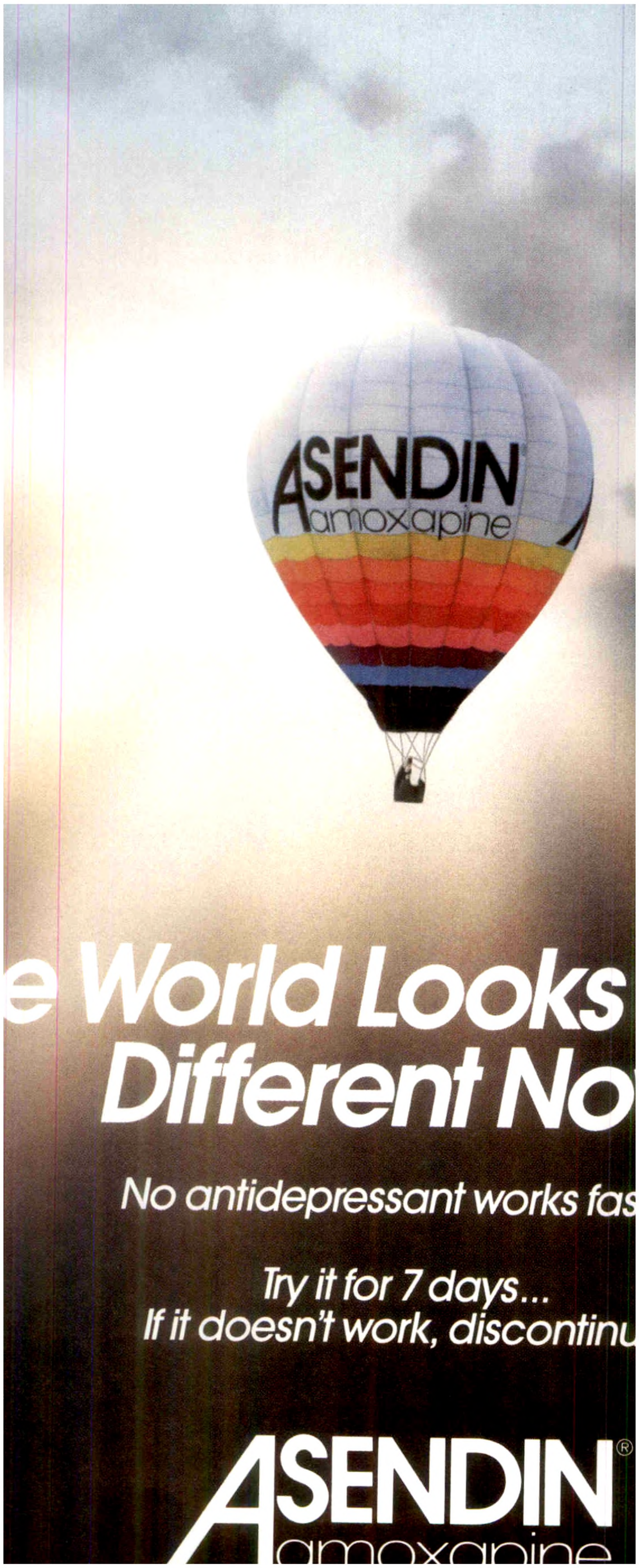
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BRIEF SUMMARY
ASENDIN® amoxapine Tablets, 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. Information for the patient: It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. Drug interactions: See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. Therapeutic interactions: Concurrent administration with electroshock may increase hazards associated with such therapy. Carcinogenesis, impairment of fertility: In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. Pregnancy. Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. Pediatric use: Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies: Incidence greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: CNS and Neuromuscular—anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. Allergic—edema, skin rash. Endocrine—elevation of prolactin levels. Gastrointestinal—nausea. Other—dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence less than 1%—Anticholinergic—disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. Cardiovascular—hypotension, hypertension, syncope, tachycardia. Allergic—drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. CNS and Neuromuscular—tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. Hematologic—leukopenia, agranulocytosis. Gastrointestinal—epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. Endocrine—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other—lacrimation, weight gain or loss, altered liver function. Drug Relationship Unknown: Reported rarely, but under circumstances where drug relationship was unknown: Anticholinergic—paralytic ileus. Cardiovascular—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. CNS and Neuromuscular—hallucinations. Hematologic—thrombocytopenia, eosinophilia, purpura, petechiae. Gastrointestinal—parotid swelling. Endocrine—change in blood glucose levels. Other—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—sublingual adenitis, dilation of the urinary tract. CNS and Neuromuscular—delusions. Gastrointestinal—stomatitis, black tongue. Endocrine—gynecomastia.

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

REFERENCES: 1. Hekimian LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. J Clin Psychiatry 1978;39:633-637. **2.** Data on file, Lederle Laboratories, Pearl River, NY. **3.** Hekimian LJ, Weise CC, Friedhoff AJ Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety/depression." J Clin Psychiatry 1983;44:248-252; **4.** Paprocki J, Bustamante LS, Barcala Peixoto MP, et al: A double-blind comparison of amoxapine and imipramine in depression. A Folha Medica 1977;74:199-210. **5.** Fabre LF: The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. J Clin Psychiatry 1985;46:521-524.

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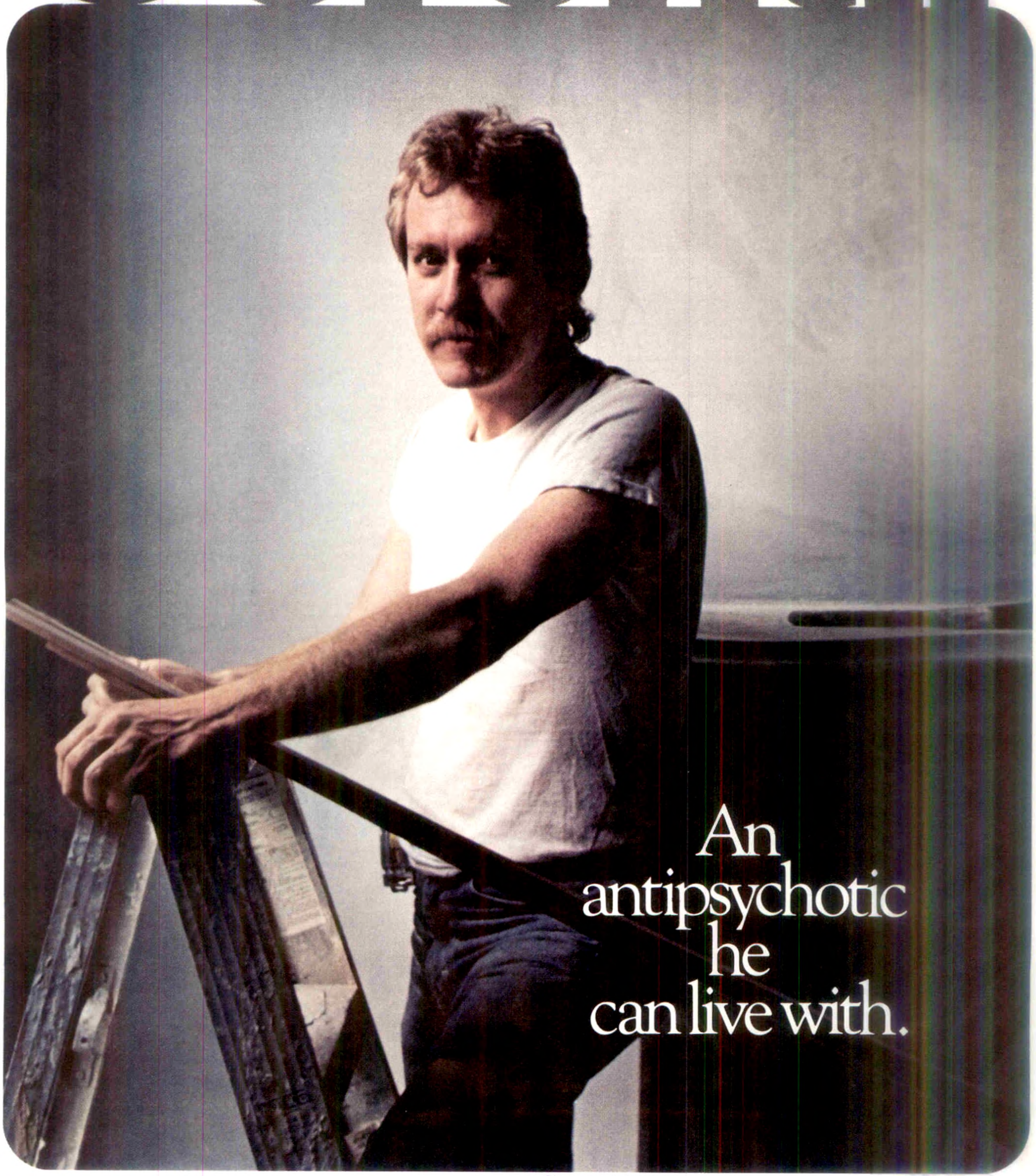
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Tablets: 10, 25, 50 and 100 mg

Concentrate: 25 mg/ml

Injectable: 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions).

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Serentil® Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Serentil® Ampuls, for intramuscular administration: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20 and 100.

Serentil® Concentrate, for oral administration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume.

Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

SE-BPI-9/85

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New! **DETERMINING MENTAL STATUS: The "Physical Examination" of Psychiatry** *by* **Martin Kantor.** Based on the premise that careful and precise diagnosis is the foundation of effective patient care, this book outlines the classic mental status examination. Chapters also cover the pathological occurrences found in each of the major syndromes and discuss how the mental status parameters change in these syndromes. *May '88, about $68.50*

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DISULFIRAM (ANTABUSE®) – A UNIQUE MEDICAL AID TO SOBRIETY: History, Pharmacology, Research, Clinical Use *by* **Ronald W. McNichol, John A. Ewing,** *and* **Morris D. Faiman.** Professionals will herein find a wealth of clinical information on an important treatment option for the disease of alcohol addiction—disulfiram (Antabuse®). This book encompasses a compilation of research on this unique medical aid, its pharmacodynamics, pharmacokinetics and toxicology. *'87, $19.75*

INVOLUNTARY CIVIL COMMITMENT OF THE MENTALLY ILL IN THE POST-REFORM ERA *by* **Robert D. Miller.** This book discusses the major definitional criteria for commitment—mental disorder, dangerousness, and need for treatment—and examines the procedural criteria of right to counsel, to remain silent, to treatment, to least restrictive environment, to refuse treatment, and access to records. *'87, $42.75*

VIOLENCE PREDICTION: Guidelines for the Forensic Practitioner *by* **Harold V. Hall.** Forensic distortion analysis, dangerous prediction pitfalls, and training in violence prediction are among the topics discussed. Unique working appendices then present prediction tasks, checklist of violence factors, assessment report format, program evaluation format, and needs assessment inventory. *'87, $29.75*

CLINICAL MANAGEMENT OF SUBSTANCE ABUSE PROGRAMS *by* **Robert J. Craig.** Focusing on the importance of the entire program versus any single treatment modality, this book addresses the major steps of substance abuse treatment. The author examines patient assessment through the use of the traditional diagnostic interview and psychological testing, covers specific models of treatment, and discusses program evaluation activities. *'87, $37.50*

New! **FORENSIC PSYCHIATRY: A Practical Guide for Lawyers and Psychiatrists (2nd Ed.)** *by* **Robert L. Sadoff.** This new edition encompasses the major changes in mental health law, criminal law, personal injury and malpractice law that have occurred over the past decade. It details the various types of cases encountered in the forensic psychiatric practice and also includes the practical aspects of working with attorneys in both criminal and civil cases. *Mar. '88, about $39.75*

New! **PSYCHOTHERAPEUTIC APPROACHES TO SPECIFIC DSM-III-R CATEGORIES: A Resource Book for Treatment Planning** *by* **Kenneth Urial Gutsch.** This book provides descriptions of specific DSM-III-R disorders, identifiable character traits, listings of current assessment instruments, and steps by which the potential for better treatment becomes possible. *'88, $36.50*

THE PSYCHOTHERAPIST-PATIENT PRIVILEGE: A Critical Examination *by* **Daniel W. Shuman** *and* **Myron F. Weiner.** The authors—a law professor and a psychiatrist—herein examine privilege and its impact in litigation. They discuss psychosocial theory and privileged communication, legal foundations of privilege and professional secret, and the uses and limitations of empirical research in the law. *'87, $29.75*

BASIC HANDBOOK OF TRAINING IN CHILD AND ADOLESCENT PSYCHIATRY *written and edited by* **Richard L. Cohen** *and* **Mina K. Dulcan.** Experts herein review and describe an integrated approach to child psychiatric training and education. They discuss the background of child and adolescent psychiatry and provide guidelines for training in such areas as psychopharmacology, developmental disabilities, pediatric consultation, and chief residencies. *'87, $68.75*

CLINICAL RESEARCH IN SCHIZOPHRENIA: A Multidimensional Approach *edited by* **Roy R. Grinker, Sr.** *and* **Martin Harrow.** This book focuses on the theoretical and diagnostic issues in relation to schizophrenia, disordered cognition, major aspects of psychopathology, and on overall prognosis and outcome. Abnormal-pursuit eye movements, thought disorder and negative deficit symptoms, long-term institutionalization and cognitive deficit, and many other topics are discussed. *'87, $55.00*

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THE CLINICAL APPLICATION OF PROJECTIVE DRAWINGS (6th Ptg.) *by* **Emanuel F. Hammer.** Intelligent and insightful, this book covers fundamentals, differential diagnosis, appraisal of psychodynamics, conflict and defense, psychological resources as treatment potentials, and projective drawing usage in therapy. The text also includes in its integrated presentation the Draw-A-Family procedure, Kinget's Drawing Completion Test, and the Eight Card Redrawing Test, among many others. *'80, $39.75*

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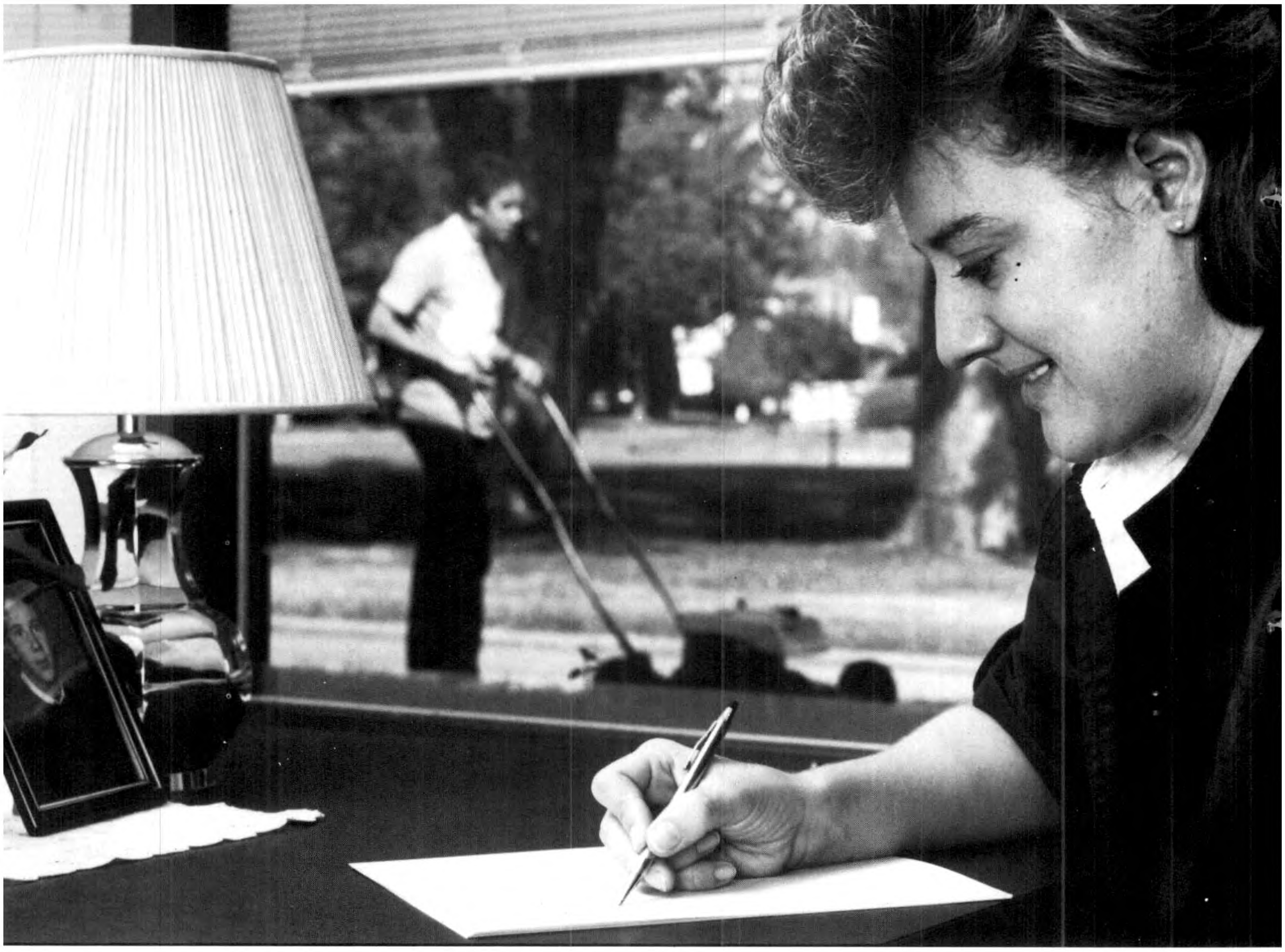

Thank You, Doctor...

Thank you, doctor, for helping us give Tommy the care he needed. Your referral to the St. Francis Homes was just the right prescription for our troubled son. His stay at St. Francis combined with your aftercare was exactly the right medicine.

Thanks to you and St. Francis, Tommy is a changed young man. After just a year in their therapy program and under their full-time supervision, Tommy is no longer the hostile and rebellious teenager we saw hanging around with the wrong crowd and getting deeper and deeper into trouble.

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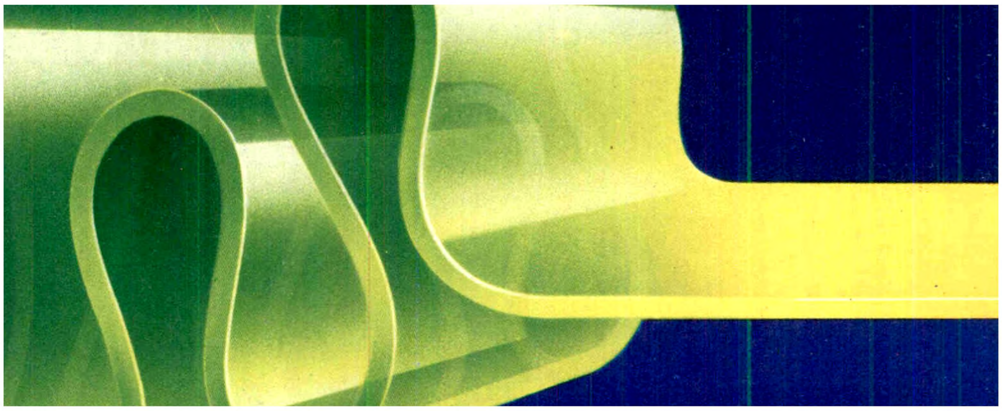

Sustained drug levels with a single monthly dose

HALDOL® DECANOATE
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the therapeutic constant in schizophrenia

Pharmacokinetic profile facilitates monthly dosing

Smooth, steady drug delivery has been shown to achieve efficacy equal to oral HALDOL, but at lower monthly doses.[1] The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about 3 weeks.[6]

The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy have, at some time, been treated with, and have tolerated well, short-acting HALDOL in order to exclude the possibility of unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

References

1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: Efficacy, safety, and dosage equivalence. *J Clin Psychopharmacol* 1986;6(No. 1, Suppl.):30S-37S.
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5. Roose K: Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. *Acta Psychiatr Belg* 1982;82:216-223.
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Please see brief summary of prescribing information on next page.

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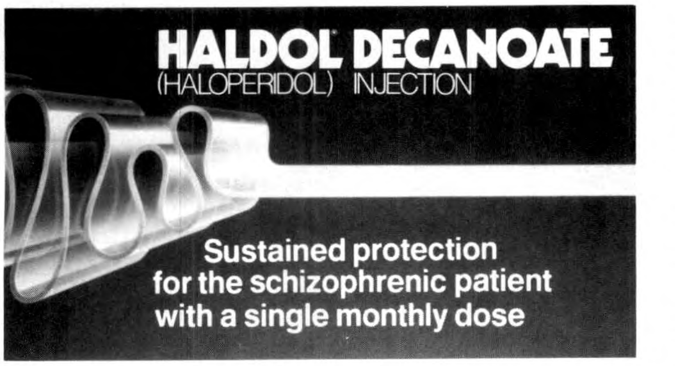

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in
those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abili
may be impaired. Alcohol should be avoided due to po

Drug Interactions: Patients receiving lithium plus h
early evidence of neurological toxicity and treatment
As with other antipsychotic agents, it should be
potentiating CNS depressants such as anesthetics, o

Carcinogenesis, Mutagenesis and Impairment of Fe
decanoate was found in the Ames Salmonella micros

Carcinogenicity studies using oral haloperidol wer
mg/kg daily for 24 months) and in Albino Swiss mice
In the rat study survival was less than optimal in all dos
for developing tumors. However, although a relatively
the study in high dose male and female groups, these
tumors than control animals. Therefore, although
absence of a haloperidol related increase in the inci
times the usual daily human dose for chronic or resist
the highest initial daily dose for chronic or resistant
increase in mammary gland neoplasia and total tumo
there was a statistically significant increase in pi
statistically significant differences in incidences of
noted.

Antipsychotic drugs elevate prolactin levels; the e
tion. Tissue culture experiments indicate that appro
are prolactin dependent *in vitro*, a factor of potential im
contemplated in a patient with a previously detected
as galactorrhea, amenorrhea, gynecomastia, and i
significance of elevated serum prolactin levels is u
mammary neoplasms has been found in rodents a
drugs. Neither clinical studies nor epidemiologic studi
an association between chronic administration of the
available evidence is considered too limited to be con

Usage in Pregnancy: Pregnancy Category C. Sa
become pregnant has not been established; use only
the fetus.

Nursing Mothers: Infants should not be nursed duri

Pediatric Use: Controlled trials to establish the
administration in children have not been conducted.

Adverse Reactions: Adverse reactions following t
Decanoate are those of HALDOL. Since vast expe
adverse reactions are reported for that compound a
injectable medications, local tissue reactions have be

CNS Effects: Extrapyramidal Reactions—Neuromu
reported frequently, often during the first few d
Parkinson-like symptoms which when first observed
usually reversible. Other types of neuromuscular rea
sia, hyperreflexia, opisthotonos, oculogyric crises)
were often more severe. Severe extrapyramidal re
doses. Generally, extrapyramidal symptoms are do
doses and disappear or become less severe when th
be required. Persistent extrapyramidal reactions hav
discontinued in such cases. *Withdrawal Emergent N*
short-term antipsychotic therapy is generally unevent
treatment experience transient dyskinetic signs aft
are indistinguishable from "Tardive Dyskinesia" exce
withdrawal will reduce the occurrence of these s
HALDOL should be gradually withdrawn. *Tardive D*
HALDOL has been associated with persistent dy
consisting of potentially irreversible, involuntary, d
patients on long-term therapy or may occur after d
appears to be greater in elderly patients on high-dos
are persistent and in some patients appear irrev
rhythmical involuntary movements of tongue, face
puffing of cheeks, puckering of mouth, chewing mo
panied by involuntary movements of extremities a
treatment for tardive dyskinesia; antiparkinson age
this syndrome. It is suggested that all antipsychotic
appear. Should it be necessary to reinstitute treatm
switch to a different antipsychotic agent, this syndro
fine vermicular movement of the tongue may be a
medication is stopped at that time the full syndrom
dystonia, not associated with the above syndrome,
characterized by delayed onset of choreic or dystoni
potential of becoming irreversible. *Other CNS Effects*
agitation, drowsiness, depression, lethargy, headach
exacerbation of psychotic symptoms including hallu
which may be responsive to drug withdrawal and/or

Body as a Whole: Neuroleptic malignant syndrom
been reported with HALDOL. (See WARNINGS for
vascular Effects: Tachycardia, hypotension, hyperte
Reports of mild, usually transient leukopenia and leu
counts, anemia, or a tendency toward lymphomono
only in association with other medication. *Liver Eff*
Dermatologic Reactions: Maculopapular and acneif
vity, loss of hair. *Endocrine Disorders:* Lactation,
irregularities, gynecomastia, impotence, increase
hyponatremia. *Gastrointestinal Effects:* Anorexia, co
sia, nausea and vomiting. *Autonomic Reactions:*
diaphoresis, and priapism. *Respiratory Effects:* La
depth of respiration. *Special Senses:* Cataracts, retin
of sudden and unexpected death have been repo
HALDOL. The nature of the evidence makes it impos
HALDOL played in the outcome of the reported case
cannot, of course, be excluded, but it is to be kept in
occur in psychotic patients when they go untre
antipsychotic drugs.

**IMPORTANT: Full directions for use should be rea
administered or prescribed.**

**For information on symptoms and treatment of
tion.**

The short-acting HALDOL injectable form is in
patients with moderately severe to very severe symp

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THE BRITISH JOURNAL OF PSYCHIATRY

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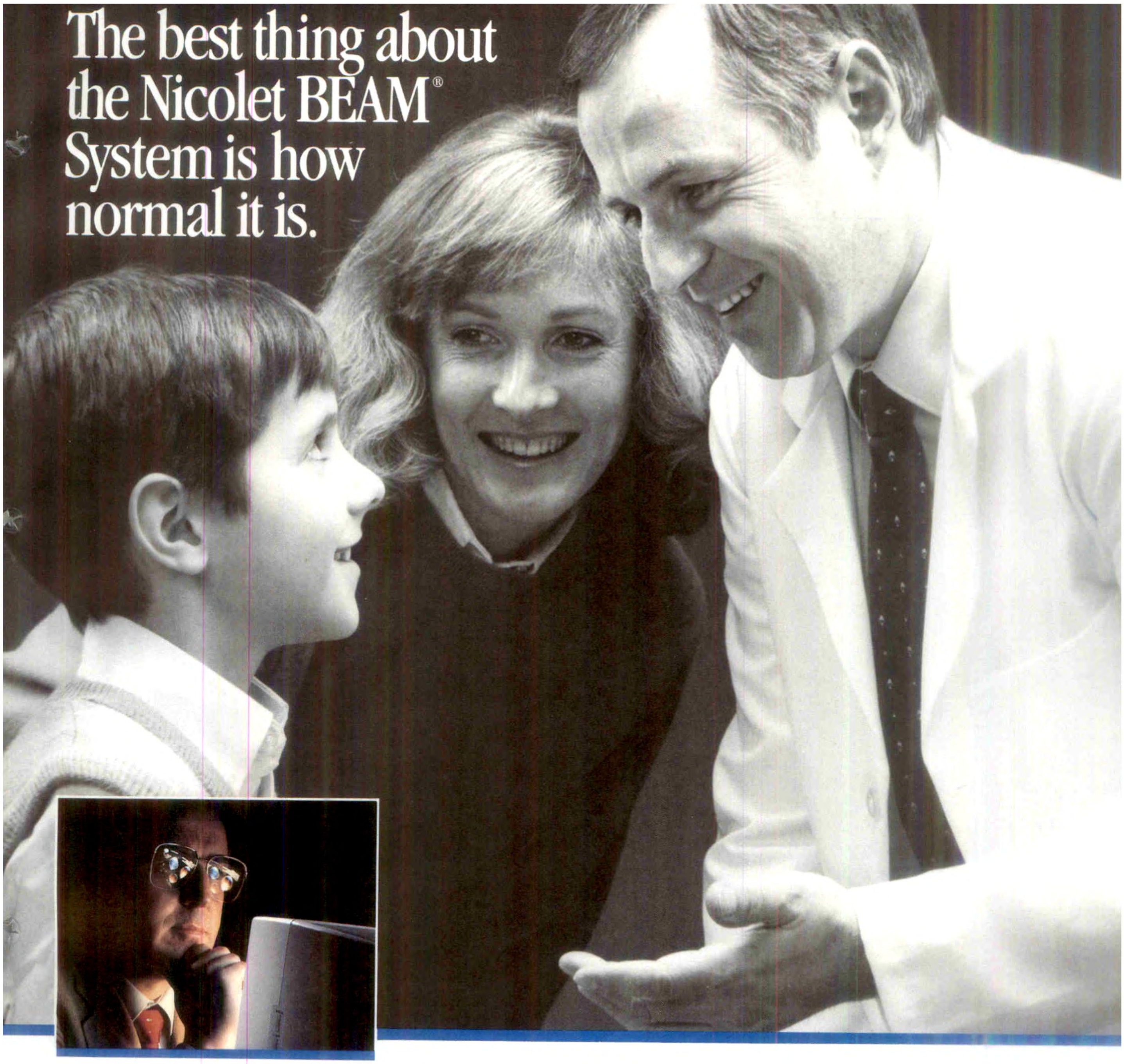

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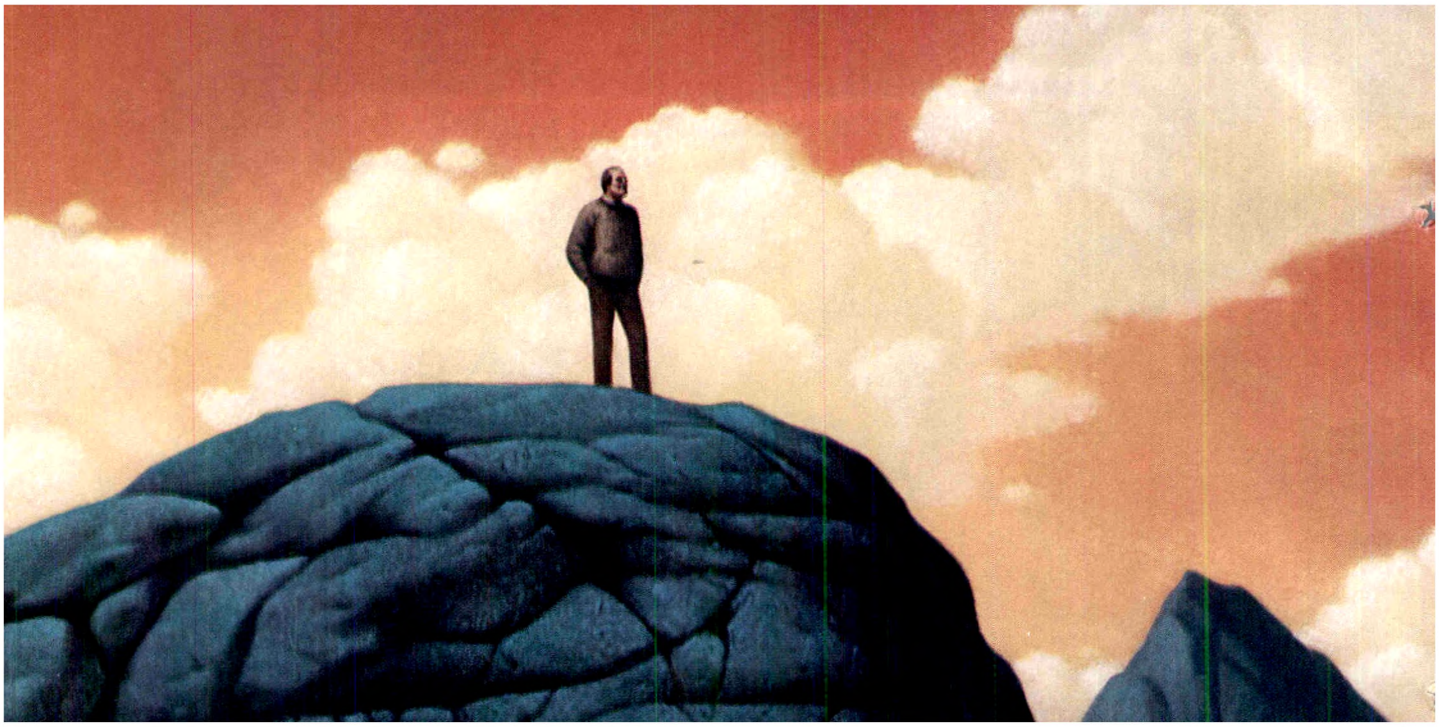

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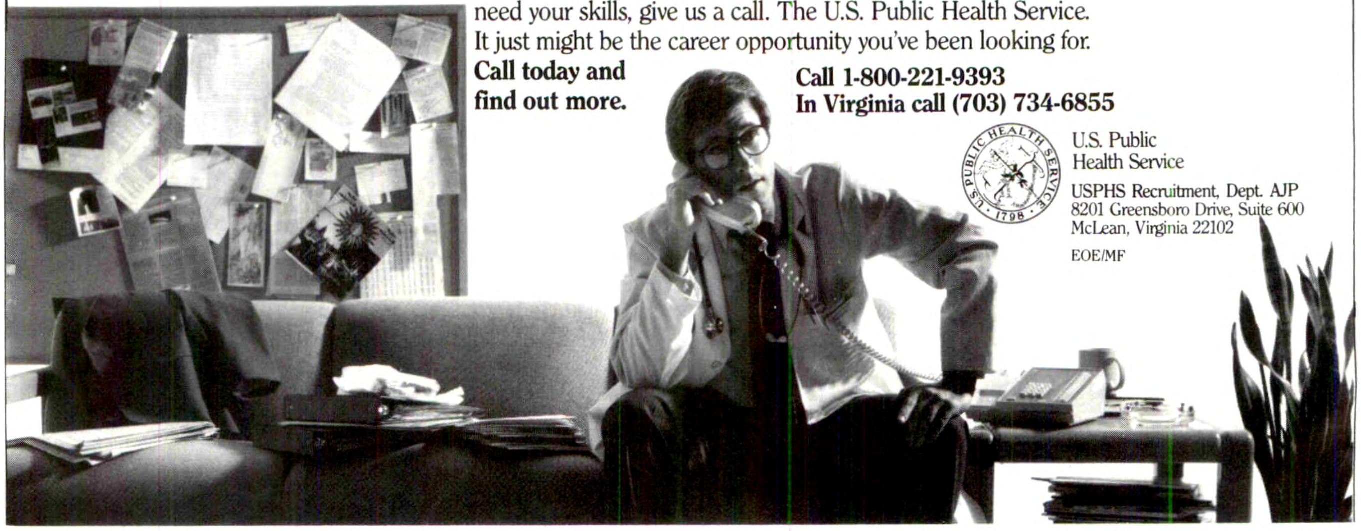

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Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

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NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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